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ORIGINAL ARTICLES

ON THE DIAGNOSIS OF HEMORRHAGE IN MAN

A STUDY OF VOLUNTEERS BLED LARGE AMOUNTS

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That hemorrhage can be diagnosed by a rapid pulse and a low blood pressure is a concept so widely accepted that it seems almost an impertinence to question it. We were first led to do so by observations made on patients after operation on the neurosurgical service. White's observations[16] had disclosed that the loss of blood in major neurosurgical operations was much larger than had been suspected, and his estimates of the amount lost, from 1 to 2 liters, were confirmed in this hospital by Webster.[14] However, after operations in which much blood was undoubtedly lost, some patients showed none of the signs ordinarily expected after so large a hemorrhage.

Further reflection on this situation forced us to admit that exact knowledge of the symptoms following hemorrhage in man was scanty and to wonder by what means this condition could be diagnosed in patients not seen until after hemorrhage had taken place. This matter seemed of especial importance in war time; and it was, therefore, decided to bleed volunteers and study the manifestations which followed in order to improve our ability to detect the abnormalities following hemorrhage. Furthermore, such a project would throw light on the important question of how much blood donors should be asked to give with due regard to their safety.

While therapeutic bleeding is no longer commonplace, the removal of 400 to 500 cc. from blood donors has become so. The effect of bleeding in amounts larger than this has been studied in 6 normal subjects by Ebert, Stead and Gibson,[1] and in 27 convalescents by Wallace and Sharpey-Schafer.[13] Our results confirm many features of these reports. Our studies also included estimations of cardiac output from ballistocardiograms and many observations on the effect

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of the erect position on the signs and symptoms which followed acute hemorrhage. Finally, gaining confidence with experience, certain of the authors volunteered to be bled until serious symptoms were produced, giving us a unique opportunity to study the situation near the breaking-point.

The investigation here reported was initiated by Shenkin, Cheney, Govons, and Starr, and a preliminary report of their results has already been published.[7] But, as Dr. Govons' work took him to another city, the advantage of his collaboration was confined to the first part of the study. Somewhat later, Hardy and Fletcher, investigating blood substitutes in the same laboratory and with the same apparatus, tried these agents on volunteers subjected to controlled hemorrhage and so obtained data on hemorrhage as a by-product of their greater interest. The detailed report of their experience with blood substitutes will be made later, but their observations on hemorrhage have been included here.

From the data obtained by both these groups, one can draw a picture of the effect of uncomplicated hemorrhage on healthy men. This picture proved to be quite different from our expectations and we hope that our experience may be of use to those charged with the care of soldiers who have bled as a result of wounds.

Technique. The volunteers were chiefly young adult males who believed themselves to be in good health. Those bled 500 cc. usually donated their blood to the hospital blood bank. When larger amounts were withdrawn, after the period of observation, blood volume was restored by using either the blood previously withdrawn or a blood substitute. There were no untoward after-effects of any kind.

After reaching the laboratory, the subjects rested on the horizontal ballistocardiograph for 15 minutes or longer before the first set of observations was made. They were then bled from a convenient antecubital vein into a bottle containing citrate. The bleeding, done under mild suction, required from 4 to 20 minutes. Observations were recorded for varying intervals before restoration of the blood volume.

Cardiac output was calculated from the ballistocardiograms by the area method[8] and the results have been reported as percentage deviations from the empirical average normal.

Venous pressure was measured through the needle used for the venesection, using a manometer overfilled with citrate solution, the fluid being allowed to run into the vein as far as it would. No reading was accepted unless the top of the column fluctuated with respiration. The error due to resistance in the tubing and needle was estimated and a small correction was applied to the observed values. An imaginary line, parallel to the table and halfway between the anterior chest wall and the table, was employed as a base line.

The hematocrit results were measured on citrated blood in Wintrobe tubes after having been centrifuged ½ hour at 2500 R.P.M. Blood proteins were estimated by a Kjeldahl semi-micro technique. Both these estimations were performed under the direction of Dr. C. Riegel in the Harrison Laboratory for Surgical Research.

The methods of Fisher[2] were employed in the statistical analysis of certain results. In this paper, the word "significant" is always used in the statistical sense; that is, to indicate that the probability is less than 5 in 100 that the result obtained was due to chance.

The 23 cases studied by Shenkin, Cheney, Govons, and Starr were examined supine and erect, both before and after the hemorrhage. Ballistocardiograms

in the upright position were taken routinely at the beginning of the investigation but, after hemorrhage, most were so distorted by the subject's inability to stand still that cardiac output could not be estimated. We were usually forced, therefore, to be content with estimations of blood pressure and pulse rate when the subjects stood. Hardy and Fletcher's first 9 subjects were studied only when supine; the last 2 were studied in both positions.

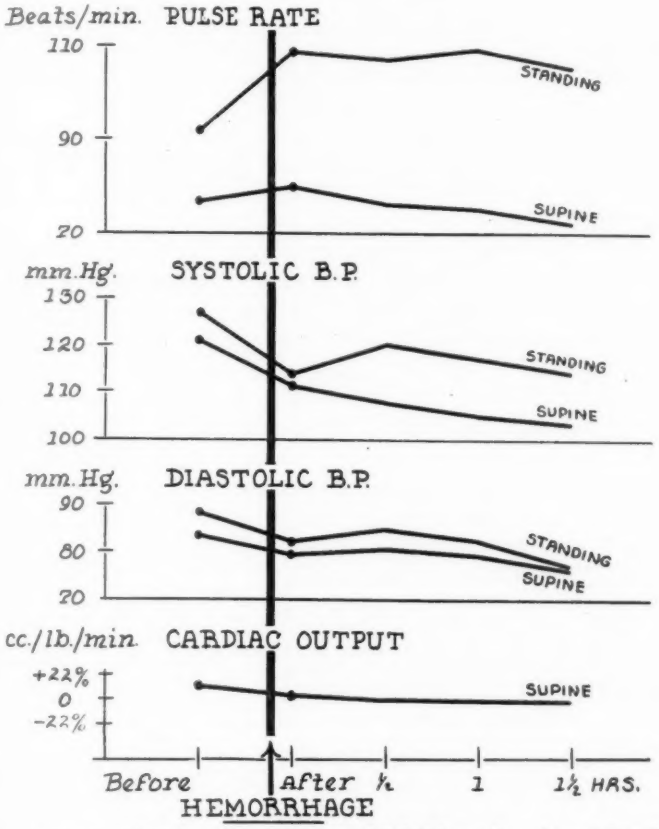

FIG. 1.—Average values found in 18 subjects bled 500 cc. (*i. e.*, from 2.5 to 3.8 cc. per pound body weight).

Results. OBSERVATIONS ON SUBJECTS BLED APPROXIMATELY 500 CC. There were 18 subjects in this group and the amount bled ranged from 2.5 to 3.8 cc. per pound of body weight, or roughly 10% of the circulating blood volume. The average values of all observations are given in Figure 1. In interpreting these results, it must be recalled that anyone about to be subjected to a hemorrhage or other unaccustomed procedure is under psychologic tension which passes off as the event proceeds. The senior author's large experience with medical students given drugs, especially with those given inert solutions when they expected drugs, demonstrates this clearly. The slow downward trend of the average values shown in Figure 1 needs no other interpretation than this.

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The systolic blood pressure, measured with the patient supine, fell on the average 13 mm. after the hemorrhage, and this is highly significant. But this value was greatly influenced by the results obtained in 2 subjects in whom it fell 48 and 30 mm. and then quickly recovered. There was also 1 subject, evidently much excited, whose systolic pressure, 150 mm. Hg before hemorrhage, fell to normal and remained there after the strain was over. If these 3 cases are omitted, the average diminution was only 9 mm. Hg immediately after the hemorrhage, but this is still significant. There was a slight downward trend for the remaining period of observation.

The average systolic pressure when the subjects stood, differed very little from that found when they were recumbent. The average standing value diminished 14 mm. Hg after the hemorrhage, and this is significant.

In supine subjects the average *diastolic blood pressure* did not change significantly after the hemorrhage; but when the subjects stood, this pressure averaged 7 mm. less after the hemorrhage, and this difference is significant. The average pulse pressure was not changed materially by the hemorrhage.

When the subjects were supine, the average *pulse rate* did not change significantly after hemorrhage of 500 cc.; but when erect, the average increase after hemorrhage was conspicuous and highly significant. This increase was maintained during the period of observation. Before hemorrhage, the average pulse rate increased 15% on arising, a change within the normal range; but immediately after hemorrhage it increased 36%, and 1 hour later 40%, both these values being abnormal.[9,11] Despite the increase found in the great majority, on 4 occasions the pulse rate in the erect position markedly diminished after the bleeding and all these patients collapsed soon afterwards. The significance of this finding will be discussed later.

The average *cardiac output* and *stroke volume* changed very little after the 500 cc. hemorrhages. These measurements were made only in the supine position, since, when the subjects stood erect after the hemorrhage, there was usually sufficient tremor to ruin the record of the cardiac impacts.

Observations on Subjects Bled Approximately 1 Liter. After hemorrhages of this magnitude, 11 subjects were observed for about ½ hour or under; 5 for 3 hours; and 1 for 24 hours before restoration of blood volume. Records of 2 typical cases are given in Figures 2 and 3, and the data are to be found in Tables 1, 2 and 3.

Hemodilution was followed by means of the hematocrits. In 11 cases (Table 1), samples were taken before and within 25 minutes of the cessation of bleeding; in these the reduction of corpuscle volume averaged 2%. In 3 cases, the samples were taken at hourly intervals after the hemorrhage was over; the reduction at the 1st hour averaged 3.7%, at both the 2nd and 3rd hours, 3.3%. The results obtained on J. D. H., studied for 20 hours, are recorded in Table 2. As expected, a slowly increasing dilution of blood took place after hemorrhage, but

it was far from sufficient to restore blood volume in any of our cases during the period of observation.

Observations Made While the Subjects Were Recumbent. In the great majority the *blood pressure* diminished after the hemorrhage, but in

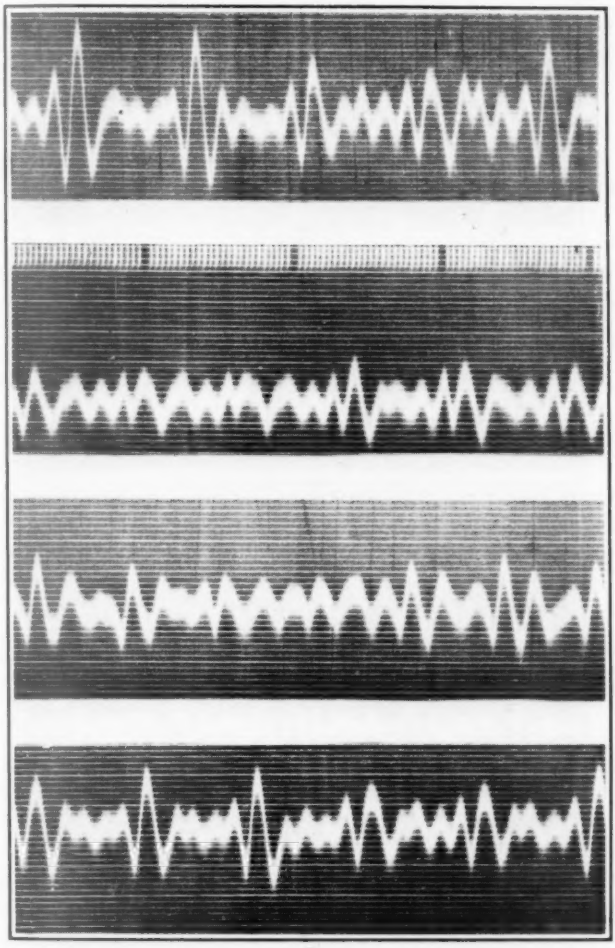

FIG. 2.—Ballistocardiograms on T. D., age 37, ht. 5′ 9½″, weight 182 lbs. The reproduction is ⅔ actual size.

Top record obtained before bleeding at 2 P.M. Pulse rate 75 per min., blood pressure 124/86 mm. Hg. Cardiac output per minute deviates from expected average normal by +13% (normal limits ±22%). *Second record* at 3:12 P.M. Pulse 82. B. P. 124/92. Cardiac output −30%. *Third record* at 4:45. Pulse 87. B. P. 120/98. Cardiac output −24%. Between 5:02 and 5:47, 970 cc. of blood was replaced. *Last record* at 6:07. Pulse 82. B. P. 124/90. Cardiac output −9%.

2 subjects it remained essentially unchanged; in 1 it increased somewhat, perhaps due to the involuntary muscular movements occurring at this time. In most cases the minimum was reached just after bleeding had ceased; but in some, it occurred from ½ to 1 hour later.

After the minimum had passed, the blood pressure increased slowly. If first seen 2 hours after the event, the hemorrhage would never have been suspected from the blood pressure readings taken while the subjects lay at rest.

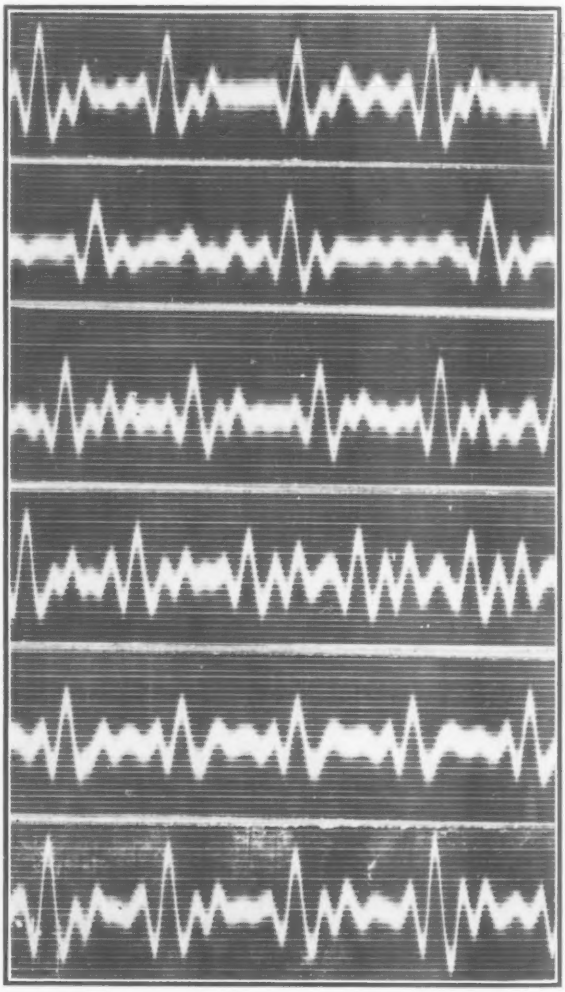

FIG. 3.—Ballistocardiograms on J. J., age 24, ht. 5′ 7″, weight 137 lbs. The reproduction is $\frac{1}{2}$ actual size.

First record obtained before bleeding at 6:48 P.M. Pulse rate 70, blood pressure 110/68. Cardiac output +4%. Between 6:52 and 7:03, 1090 cc. of blood were withdrawn. *Second record* started at 7:06. While the record was running, the pulse rate diminished from 60 to 46, the cardiac output from −9% to −26%. The blood pressure taken at the end was 92/54. Symptoms of nausea and vomiting, pallor and sweating appeared. *Third record* at 7:10. By this time the symptoms had largely passed off. Pulse rate was 70, B. P. 120/70. Cardiac output −9%. *Fourth record* at 9:30. Pulse 80, B. P. 110/64. Cardiac output did not deviate from the expected normal. Between 9:37 and 10:00, the blood withdrawn was replaced. *Fifth record* at 10:00. Pulse 78, B. P. 124/78. Cardiac output +9%. *Sixth record* at 11:00. Pulse 72, B. P. 120/68. Cardiac output +13%.

The *pulse rate*, after these large hemorrhages, exceeded 100 in no case save the subject who had had a corresponding tachycardia before the event. The rate increased materially in only 3 subjects, and in 2 of these the increase was temporary. In contrast to this, the rate slowed materially in 9 subjects and this was accompanied by symptoms to be described. That slowing of the pulse was more common than acceleration greatly surprised us. In subjects first seen after the event, the hemorrhage could never have been diagnosed from the pulse rate.

TABLE 1.—THE CIRCULATION BEFORE AND JUST AFTER BLEEDING LARGE AMOUNTS; DATA OBTAINED WHILE THE SUBJECTS WERE RECUMBENT

Name and age	Height, weight (lbs.)	Amount	Blood pressure, mm. Hg.	Venous pressure, cm. H_2O	Heart rate, per min.	Cardiac output, deviation from av. norm.	Remarks
T. K.	5′ 9″	Before	96/70	11	74	− 4%	
40	185	After bleeding 1200 cc. in 15 min.	84/64	12	92	− 9%	
J. A. R.	6′ 1″	Before	128/68	15	66	+13%	
22	180	After bleeding 1065 cc. in 18 min.	130/70	15	69	− 4%	
C. T. M.	5′ 7″	Before	120/78	16	70	+ 4%	
18	135	After bleeding 900 cc. in 10 min.	58/40	12	53	−13	Sweating, faint
B. B.	5′ 8″	Before	114/60	14	77	+61	
38	150	After bleeding 1020 cc. in 8 min.	100/60	..	77	+30	
E. T.	5′ 7″	Before	130/80	13	89	+22	
38	165	After bleeding 1050 cc. in 8 min.	.....	..	45	−39	Fainted (see text)
H. G.	5′ 8″	Before	118/70	14	71	+17	
36	151	After bleeding 1000 cc. in 20 min.	68/34	9	58	0	Slight nausea
R. W. C.	5′ 8″	Before	120/60	14	67	−17	
25	196	After bleeding 1020 cc. in 15 min.	120/80	12	71	−13	
L. J.	5′ 11″	Before	150/80	17	112	+48	
27	160	After bleeding 1090 cc. in 14 min.	130/80	15	111	+48	
W. A. C.	5′ 10″	Before	130/80	..	74	+17	
25	167	After bleeding 920 cc. in 15 min.	70/40	..	47	−17	Weak, nausea
A. G. F.	6′ 2″	Before	115/70	..	76	+11	
26	170	After bleeding 1050 cc. in 17 min.	96/50	..	52	−23	Sweating, pallor, slight nausea
T. N.	5′ 11″	Before	112/66	10	76	−4	
25	152	After bleeding 1000 cc. in 15 min.	124/76	..	..	..	Unconscious, extremities twitching and moving. Atropine 0.7 mg. I. V., revived rapidly
					60	−15	5 min. later, quiet and conscious
			70/40	10	60	−18	10 min. later

Venous pressure was estimated in only 7 subjects. There was either a small diminution or no change after the hemorrhage. These data are recorded in Table 1.

TABLE 2.—OBSERVATIONS MADE ON J. D. H. (AGE 25; HT. 5'11"; 160 LBS.); BEFORE AND AFTER BLEEDING 1115 CC. OR 15 CC. PER KILO. THE OBSERVATIONS HERE RECORDED WERE ALL MADE WHILE THE SUBJECT WAS RECUMBENT AND AT REST

Time	Pulse rate (per min.)	Blood pressure (mm. Hg)	Cardiac output deviation (%)	Hemtaocrtis (% RBC)	Plasma protein (gm./100 cc.)	Remarks
1.33 P.M.	70	114/74	+13	40.5, 41	6.93	After ½ hr. rest
1.45	..	....	....	....	....	Bleeding begins
1.55	84	116/80	....	....	....	500 cc. out
2.04	..	....	....	....	....	Bleeding over, 1045 cc. out
2.05	45	96/60	−39	....	....	Nausea, sweating, weak, pale and faint
2.10	60	70/40	....	40.5, 39	6.76	Symptoms continue
2.12	76	84/62	....	....	....	Better
2.17	72	98/64	− 9	....	....	Dry mouth, mild headache
2.34	73	100/68	− 4	39, 39	6.61	Drank 200 cc. water
3.34	76	104/68	− 9	37, 37	6.36	Feeling well while recumbent
5.34	82	108/70	0	38, 40	6.38	Drank 200 cc. water
6.25	..	....	....	....	....	After supper, 500 cc. fluid
10.00	81	112/78	+13	36, 36	6.20	
11.00	..	....	....	....	....	After sandwich, coffee and water; 400 cc. fluid
1.20 A.M.	72	110/70	+ 4	36	6.08	
1.30	..	....	....	....	....	To bed; wakeful, took 180 mg. Na amytal
9.17	80	102/60	....	36.5, 36	6.76	
12.00	..	....	....	....	....	Light lunch
2.13 P.M.	78	110/80	+17			
2.30	..	....	....	....	....	Up and about
3.30	..	....	....	....	....	Replacement of blood started
5.15	..	....	....	....	....	1035 cc. blood in and about 100 cc. saline
5.20	68	100/78	+17			

TABLE 3.—EFFECT OF ARISING ON SUBJECT J. D. H. (AGE 25; HT. 5'11", 160 LBS.); AFTER LOSING 1115 CC. BLOOD AND AFTER ITS REPLACEMENT

Time	Pulse rate (per min.)	Blood pressure (mm. Hg)	Cardiac output deviation from av. normal	Remarks
2.04 P.M.	..	.....	.....	Bleeding over 1045 cc. out
3.51	80	110/72	.....	Feels well when recumbent
3.53	98	100/74	.....	Sitting on edge of bed
3.54	76	.....	.....	Sweating, nausea, faintness forced recumbency
5.45	78	108/70	.....	Lying comfortably at rest
5.46	..	.....	.....	Sat up at edge of bed
5.47	88	90/70	.....	Dizzy
5.48	88	70/50	.....	Nausea and faintness forced recumbency
1.30 A.M.	72	110/70	.....	Lying at rest
1.31	..	.....	.....	Sitting up
1.32	96	98/74	.....	
1.38	88	94/70	.....	No unusual sensations
1.40	88	88/64	.....	Stood up
1.41	..	70/50	.....	Dizzy and faint, forced to lie down
9.17 A.M.	80	102/60	.....	Lying at rest
9.18	104	86/70	.....	Sat up, no symptoms
9.24	96	96/60	.....	Still sitting, no symptoms
9.25	120	90/74	.....	Standing
9.29	108	80/64	.....	Still standing, no symptoms
2.13 P.M.	78	116/64	+18%	Lying comfortably
2.16	102	100/80	+26%	Standing 2 min., no difficulty
5.10	..	.....	.....	Blood replaced
5.15	65	100/70	+18%	Lying at rest
5.20	72	100/76	−17%	Standing 2 min.

The deviation of serial estimations of *cardiac output*, calculated from ballistocardiograms, has been carefully studied by Tanner;[12] the standard error of the second estimation being 4.8%. For this reason, if an estimation differs from its predecessor by more than 9.6%, the difference is significant. Therefore, the cardiac output diminished significantly after hemorrhage in almost all our subjects. However,

in only 5 was the cardiac output ever found below the empirical lower normal limit, 22% from average normal, and all these cases suffered from acute symptoms at this time. In the absence of such acute attacks, the estimations of cardiac output would have provided no clear evidence of the preceding blood loss in the great majority of instances.

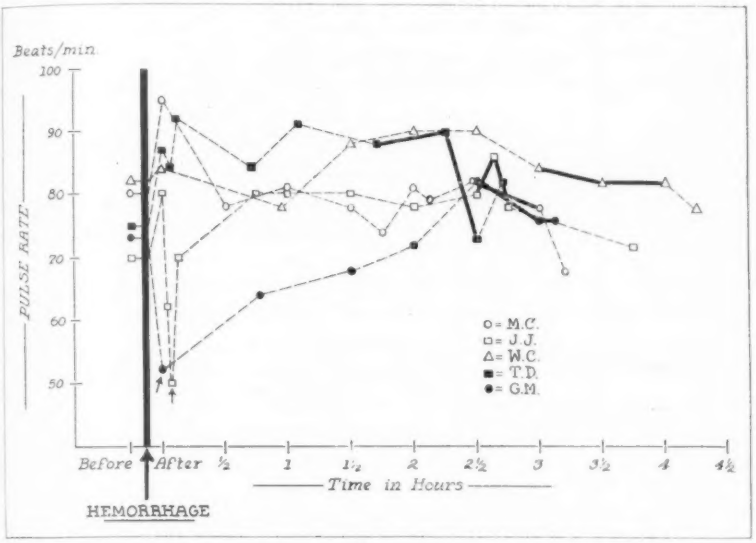

FIG. 4.—Pulse rates taken while the subjects were recumbent and at rest in 5 normal persons, before and after bleeding of approximately 1000 cc., and after replacement of the blood. The heavy line connecting the symbols indicates the period during which the blood was being replaced. The arrows indicate points where the subjects suffered from acute symptoms as described in the text.

Abnormalities Found When, After a Large Hemorrhage, the Subject Arose. In the 6 subjects (see Figures 4, 5, and 6, and Table 3), observations were attempted when they stood erect, as well as when they were recumbent. But the 4 subjects, bled the largest amounts, 5.7, 6.3, 7.0, and 7.9 cc. per pound of body weight, could not tolerate the erect position because of faintness and dizziness, soon followed by collapse, if they were not immediately laid flat. The other 2 subjects, bled smaller amounts in proportion to their weight, 5.3 and 5.4 cc. per pound, were able to stand without collapse, but the abnormal increase in their *pulse rates* on arising indicated the strain to which the circulation was subjected. Thus in 1 of these cases, the pulse rate before the hemorrhage was 82 recumbent and 93 after arising; the corresponding figures immediately after, and at ½ hour intervals after the hemorrhage, were 84 and 124, 78 and 124, 88 and 112, 90 and 120. In the other case, the pulse rate was 75 recumbent and 86 after arising before the hemorrhage. Immediately after it, these rates were 84 and 96; at ½ hour intervals thereafter, they were 84 and 156, 82 and 156, 87 and 148. After the return of the blood, the pulse rates in the 2

positions closely approximated those recorded before the hemorrhage in both these cases.

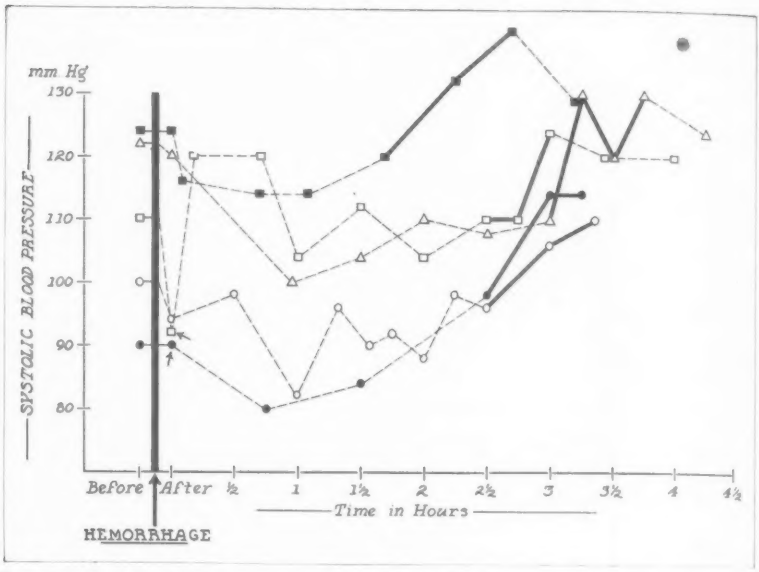

FIG. 5.—Systolic blood pressure of 5 subjects bled approximately 1000 cc. Other symbols as in Figure 4.

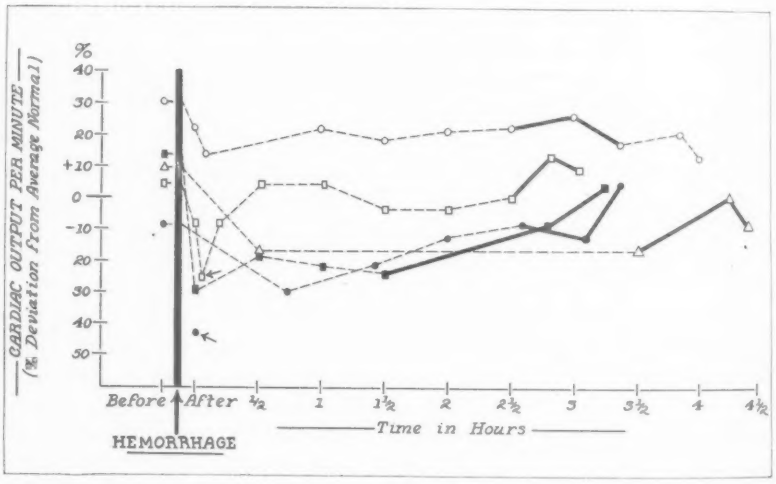

FIG. 6.—Cardiac output per minute, expressed as a percentage deviation from the normal average in 5 subjects bled approximately 1000 cc. Symbols as in Figure 4.

In the 4 who became faint, a sharp acceleration of the pulse was noted immediately after arising but, almost before a count could be made, the pulse slowed markedly and values below 50 were regularly obtained as the symptoms of collapse manifested themselves.

In 2 who did not faint on arising, the *systolic blood pressure*, which before the hemorrhage changed less than 5 mm. when they arose, after the hemorrhage fell, from 10 to 30 mm. Hg in every estimation save 1, when an increase of 6 mm. was recorded. Diastolic pressure in either position was not greatly affected by the hemorrhage in these subjects.

In the 4 who became faint, the blood pressure tended to collapse as the symptoms appeared, but the exigencies of the moment permitted few estimations. The *acute symptoms* which so many subjects experienced when they stood upright, and a few when they lay recumbent, differed only in their severity. The picture will be described in detail under later headings.

Observations on Subject J. D. H., Bled Over 1 Liter and Observed for 24 Hours. After the rest of the studies had been completed, 1 of the authors volunteered for a more exacting experiment. It was planned to bleed him until the production of severe symptoms and then follow the progress of spontaneous recovery for 24 hours. The objective results of this experience are recorded in Tables 2 and 3. These and the subjective sensations which accompanied them deserve detailed description, as the subject was a trained observer.

After control observations, bleeding progressed uneventfully until about 750 cc. had been withdrawn. Then the subject noted waves of tingling going lengthwise over his body and these were soon followed by generalized tingling. Nothing further was noted until after 1035 cc. had been withdrawn. Promptly thereafter, nausea and faintness were noted while vision became dim. The observers now noted pallor, coldness of hands, hyperventilation, restlessness, generalized sweating, bradycardia, and diminished blood pressure. From the record now taken, cardiac output was calculated to be about $\frac{1}{2}$ that found before the hemorrhage. During this period of severe symptoms, the subject noted that his respiratory efforts markedly affected his sensations; hyperventilation improved the symptoms, and as soon as he stopped exerting himself, faintness overwhelmed him. Also he felt forced to keep moving and so flexed his legs and moved them from side to side, because he did not dare to lie still. Finally his hands went into carpal spasm, and the observers demonstrated Chvostek's sign.

After about 5 minutes, the symptoms began to improve spontaneously, the carpal spasm and positive Chvostek's sign persisting longer than the other manifestations. Blood pressure and cardiac output increased with improvement in the symptoms. Finally the subject noted only a dry mouth, thirst, and a mild headache, which gradually passed off. He was then comfortable as long as he lay at rest. During this period, both cardiac output and blood pressure, while lower than before the hemorrhage, were not outside empirical normal limits.

However, when he attempted to sit on the side of the table, the pulse rate first accelerated and then slowed markedly. The blood pressure diminished until it could not be obtained. These objective phenomena were accompanied by sweating and sensations of nausea and faintness which forced him to lie down within a few moments.

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The condition of comfort when at rest and horizontal, but inability to sit or stand upright, persisted for about 12 hours, during which he drank 1300 cc. of fluid. Twelve hours after the hemorrhage, he could sit upright without symptoms, but he was still unable to stand.

Eighteen hours after the hemorrhage, the subject could both sit and stand without symptoms and considered himself well enough to be up and about. He was, however, weak and suffered from marked dyspnea on exertion. To the observers, he looked and acted like a sick man. He was able to stand without symptoms; but it is to be noted that the pulse rate increased to over 100 whenever he arose, and that the cardiac output, when he stood, was calculated to exceed the resting value. This condition lasted about 8 hours, or until the blood was replaced. The total amount of blood removed, including the samples taken for analysis as well as the initial bleeding, was 1115 cc.

After replacement of a liter of blood, the subject felt restored to normal. On arising now, the pulse rate was only 72 and he was able to stand without symptoms, although the cardiac output diminished.

Discussion. Our results permit us to describe the signs and symptoms of uncomplicated hemorrhage occurring in healthy men.

After a small hemorrhage, the abnormalities encountered may be described as the *1st stage*. In this, the subject has no symptoms when he is recumbent or standing at rest. However, as soon as he arises, an abnormal increment of pulse rate takes place and blood pressure may diminish abnormally. Such subjects are able to go about their business, but they feel weak and notice dyspnea on exertion.

If the hemorrhage be larger, the condition resulting may be described as the *2nd stage*. In this, the subject still has no symptoms and exhibits no abnormality of the circulation as long as he is recumbent and at rest. But as soon as he sits or stands upright, he is seized by a group of acute symptoms characterized by faintness and syncope and accompanied by bradycardia, the group described in detail below.

If the hemorrhage be larger still, the subject, with very little warning, enters the *3rd stage*, and suffers from acute symptoms while he is recumbent. The observers find diminished blood pressure, marked bradycardia, pallor, sweating, hyperpnea, and restlessness. The subject experiences coldness of the extremities, nausea, dizziness, faintness, and he may lose consciousness.

If bleeding be arrested and spontaneous recovery observed, the subjects pass through the 3 stages in the reverse order.

The clinical picture found in our subjects after hemorrhages of known amount resembles closely that described by Wallace and Sharpey-Schafer,[13] who studied convalescents bled amounts similar to those we employed. It also resembles in most respects the picture seen by McMichael[3] in certain air-raid victims, and in one case of experimental hemorrhage that he reported. Syncopal attacks, such as those we observed, were also reported by Ebert, Stead, and Gibson[1] in a study in which the primary interest was in estimations of blood volume after hemorrhage. The data of the authors who have seen

patients after large hemorrhages of known amount seem to be entirely consistent.

But in contradistinction to these results is the widespread belief that hemorrhage is easily diagnosed by a rapid pulse and a low blood pressure. It is true that the authors recall cases of uncomplicated hemorrhage seen in the clinic who showed marked tachycardia. We are not certain of the cause of the difference between these observations and our results, but we have the impression that these patients had very low hemoglobin concentration. So they were probably seen after dilution of the blood had taken place. Perhaps the tachycardia may have been analogous to that so often seen in cases of severe anemia of any kind. It is to be noted that in none of our volunteers had dilution come near to restoring blood volume.

Be that as it may, our results have clearly demonstrated that large hemorrhages can occur without conspicuous effect on pulse rate or blood pressure; and so, as diagnostic criteria, these signs may be both inadequate and misleading. Three things have probably contributed to the traditional viewpoint. First, a rapid pulse and low blood pressure are characteristic of rapid hemorrhage in anesthetized animals, and this has been demonstrated to generations of medical students. The fact that the unanesthetized animal can stand a much larger loss of blood without undue acceleration of the pulse and diminution of blood pressure[4] is not so widely known to clinicians. Second, few clinicians have ever seen a hemorrhage in which they had any exact idea of the amount of blood lost, and so they were not in a position to criticize the common view. Third, many hospital cases, hemorrhage is associated with trauma; and that rapid pulse rate and low blood pressure may be associated with shock is beyond dispute.

The mechanism of these parasympathetic-like or vaso-vagal attacks is not entirely clear to us. Syncope is common among blood donors and the fact that it may occur on venepuncture before blood is drawn, or in persons watching blood drawn from others, demonstrates clearly that such attacks may be of emotional origin. Nevertheless, there was absolutely nothing in the demeanor of our subjects to suggest undue emotion. Also there is a direct relationship between the incidence of fainting and the amount of blood drawn. Five of 18 subjects fainted on standing in the group bled 500 cc., while in the group bled 1 liter, 5 of the 7 allowed to stand became so faint that they had to be immediately laid flat. This indicates a mechanism at play in our cases which is not of psychogenic origin. Wallace and Sharpey-Schafer[13] came to the same conclusion; and the results of Poles and Boycott[5] also support this view, for in their studies the incidence of syncope in donors bled 540 cc. was double that in donors bled 440 cc.

Evidence from animal experiments suggests that this mechanism is not to be attributed to stimulation of the carotid sinus, but it might be thought of as induced by anemia of the brain; for profound slowing of the heart rate sometimes follows the experimental production of cerebral anemia in certain animal experiments.[10] The cardiac output of our subjects was markedly depressed during these attacks, and it

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improved *pari passu* with the symptoms; the circulation through the brain may well have behaved similarly. But whether the bradycardia is cause or effect of the cerebral anemia, our data will not permit us to decide. Starr and Collins[10] observed that signs and symptoms preceded bradycardia in persons about to faint. These observations and the experiments of Weiss *et al.*,[15] who found that persons given atropine still suffered from syncope due to nitrites although bradycardia was prevented, suggest that cerebral anemia is primary. To one of our subjects, who had lost consciousness when bled, 0.6 mg. atropine sulfate was given intravenously. He recovered rapidly; but recovery has been rapid in other subjects not so treated and we feel that no conclusions can be drawn.

It is interesting to recall an old study of the effects of large hemorrhages in man. Our predecessor on the Faculty of this school, Dr. Benjamin Rush, relating his experiences concerning the Yellow Fever Epidemic of 1793, wrote:[6] "I bled many patients twice, and a few 3 times a day. I preferred frequent and small, to large bleedings in the beginning of September; but towards the height and close of the epidemic, I saw no inconvenience from the loss of a pint, and even 20 ounces of blood at a time. I drew from many persons 70 and 80 ounces in 5 days; and from a few, a much larger quantity. Mr. Gribble, cedar-copper, in Front Street, lost by 10 bleedings a 100 ounces of blood; Mr. George, a carter in Ninth Street, lost about the same quantity by 5 bleedings; and Mr. Peter Mierken, 100 and 14 ounces in 5 days. In the last of the above persons the quantity taken was determined by weight. Mr. Toy, blacksmith near Dock Street, was 8 times bled in the course of 7 days. The quantity taken from him was about 100 ounces."

With regard to the effect of such blood letting, Rush says: "1. It raised the pulse when depressed and quickened when it was preternaturally slow or subject to intermissions. 2. It reduced its force and frequency." These 2 statements are not consistent and evidently the effect varied in different patients, as in our results.

One wonders whether, if our hemorrhages had been larger still, a point would have been reached where the expected signs of rapid pulse and low blood pressure would have appeared while the subject was supine. Our data do not give a positive answer to this question but they demonstrate clearly that a hemorrhage carried to the point of collapse may not be accompanied by any acceleration of the pulse. In 1 subject (E. T., in Table 1), the early stages of the bleeding were uneventful but after 6.4 cc. per pound had been withdrawn, although lying supine, he suddenly lost consciousness and blood pressure could not be obtained. The pulse rate before this emergency had never been recorded as abnormally rapid, and during it the rate obtained from the ballistocardiogram was very slow. Although intravenous medication promptly restored the situation in this case, it is evident that subjects cannot be bled larger amounts with safety, and that hemorrhage can produce an alarming condition without tachycardia either before or during the event.

Obviously, therefore, we have been forced to revise our concept of the clinical picture of acute hemorrhage and of the criteria useful in diagnosing such hemorrhage in persons first seen after the event. But, before continuing this discussion one concept, suggested by previous work[11] and strongly supported by the results here described, must be reviewed.

The circulation in a standing subject requires an active mechanism of adjustment to prevent accumulation of blood in dependent parts, and to maintain the supply to the brain. This mechanism is not needed when the subject lies horizontal. For this reason drugs or other agents which influence the circulation in one position may have quite a different effect when the subject is in another. Hemorrhage is but another example of a condition which influences the circulation differently in the horizontal and vertical positions.

With this in mind criteria more adequate to diagnose acute hemorrhage in man can be formulated from our experience. If such hemorrhage is suspected and no signs of it are present while the subject is at rest, he should be placed in the upright position. Then if noteworthy hemorrhage has taken place, an undue acceleration of pulse rate, perhaps with a diminution in blood pressure or the production of a syncopal attack accompanied by bradycardia, will speedily betray the abnormality.

Conclusions. Eighteen volunteers were bled approximately 500 cc.; 17 were bled about a liter. Estimation of pulse rate, blood pressure, venous pressure, cardiac output (ballistocardiograms), and hematocrit were made before and after the hemorrhage, during the process of recovery, and often after replacement of the blood.

Cardiac output diminished very little after the loss of 500 cc. of blood; after the loss of a liter, it regularly diminished significantly, and during syncopal attacks, it diminished profoundly. After completion of the bleeding, the cardiac output slowly returned toward the value found before the hemorrhage.

The effects of hemorrhage on healthy men may be divided into 3 stages of severity. In the *1st stage* the subject is symptom-free at rest and has a pulse rate and blood pressure within normal limits. However, on arising, an undue acceleration of pulse rate and some diminution of blood pressure are found. In the *2nd stage* there are still no noteworthy abnormalities as long as the subject is recumbent and at rest. But the upright position cannot be tolerated and syncope soon overwhelms the subject if he arises. In the *3rd stage* syncopal attacks accompanied by bradycardia occur even though the subject is at rest and recumbent. These attacks seem to be of physiologic and not of emotional origin.

The old concept that acute hemorrhage can be readily diagnosed by a rapid pulse and a low blood pressure is erroneous. Recumbent subjects may be bled to the point of collapse without exhibiting conspicuous tachycardia, and during the period of severe symptoms profound bradycardia is the rule. The blood pressure usually remains

within the normal range until the symptoms of collapse begin, when it diminishes profoundly.

Hemorrhages causing no signs or symptoms as long as the subjects are recumbent can be detected by having them sit or stand upright. Then the symptoms described above will speedily betray the abnormality.

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THE EFFECT OF ARTIFICIAL RESTRICTION OF ACTIVITY ON THE RECOVERY OF RATS FROM EXPERIMENTAL MYOCARDIAL INJURY*

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Although rest in bed is the most widely used method of treatment in patients with acute myocardial disorders, there have been practically no well-controlled clinical or experimental studies concerning its value and its limitations. Present practices in the use of this method of treatment are therefore based not on scientific data but on opinions which vary widely as to the length of time during which rest should be enforced, and as to the degree to which it should be applied. Thus, in Table 1 are summarized the opinions expressed by 10 authors as to the duration of rest following myocardial infarction. Some authors believe that 2 or 3 weeks is sufficiently long for the average case, whereas others think that rest in bed for a number of months is necessary. There is a similar lack of uniformity concerning the strictness of the regime of rest, some authors believing that a patient should not

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be allowed to turn in bed, to feed himself, or even lift his head, whereas others hold that even in the acute stage it is permissible for a patient to get out of bed for a bowel movement.

TABLE 1.—OPINIONS OF VARIOUS AUTHORS CONCERNING THE OPTIMAL DURATION OF REST IN BED IN PATIENTS WITH MYOCARDIAL INFARCTION

Author	Duration of bed rest recommended for average patient	Remarks
Meakins[20]	"Many weeks or even months"	
Eggleston[7]	"Many weeks"	Patient should not be allowed to feed himself or turn himself
Clendenning and Hashinger[3]	Prolonged period	
Lewis[17]	At least 8 weeks	All voluntary movements to be avoided
Beckman[1]	8 weeks	Turning and feeding should be forbidden for 6 weeks
Smith[23]	6 to 8 weeks	Often longer
Harrison[9]	6 to 8 weeks	Elderly patients should be allowed out of bed several hours daily after 2 weeks
Christian[2]	6 weeks	
Dressler[5]	6 weeks	Much longer period when attacks of pain persist or blood pressure remains low
Leaman[14]	6 weeks	
Levine[15]	4 to 8 weeks	
Fishberg[8]	4 to 8 weeks	Prolonged rest especially important in younger patients
Dry[6]	4 to 6 weeks	Elderly subjects with favorable progress allowed up after 2 to 3 weeks
White[25]	4 weeks	Longer periods of bed rest impair morale
Mallory, White and Salcedo-Salgar[19]	4 weeks	
Reid[21]	Minimum 2 to 3 weeks	Optimal period of bed rest not yet known
Levy[16]	Until infarct has healed	Sedimentation rate and electrocardiograms provide guides to healing
Libman and Sacks[18]	Until leukocyte count is normal	
Hyman and Parsonnet[12]	Until leukocyte count is normal	Patients who become irritable with bed rest should be allowed up early

Experimental attempts at enforcing artificially induced rest on animals has not been hitherto attempted, insofar as we are aware. The effect of exercise on animals with acute myocardial injury was studied by Sutton and Davis,[24] who ligated a coronary artery in 6 dogs and observed the effects of exercise carried out on a treadmill. They found

that in the animals which began severe exercise within 3 days after the ligation, the scar which finally developed was thin and that there was a tendency toward formation of aneurysm of the left ventricle. On the other hand, in the single dog which did not undertake work on the treadmill for 6 days after the production of the cardiac infarct, the scar was firm, small, and well contracted without any thinning of the ventricular wall.

The observation that severe exercise begun as early as 6 days after the injury did not seem to impair the healing process in dogs is at variance with the usual practice of having patients with myocardial infarction remain in bed for many weeks. However, there is some evidence that the heart of the dog may heal more rapidly than that of man. Thus, Karsner and Dwyer[13] observed in dogs that experimental infarcts were nearly completely healed by the end of 3 weeks. Mallory, White and Salcedo-Salgar[19] studied the hearts of 72 patients in whom the date of onset of infarction was clearly defined from the history. They found that the small infarcts in the human hearts were almost completely healed at the end of 5 weeks; whereas the large infarcts did not reach a similar degree of healing until about 2 months had passed. They believed that the fact that nearly twice as long was required in the case of human hearts as in the case of the dog hearts for a similar degree of fibrosis and healing to take place could be accounted for by the larger size of the human hearts—and hence the larger size of the infarcts—and also by the greater abundance of collateral circulation in the normal dogs than in the patients with coronary sclerosis. A third possibility, namely, that the faster rate of healing in the dog was related to the greater activity of this animal was not considered.

The question of how long an individual should be kept at rigid bed rest following infarction or other acute injury to the heart is important, not only from the standpoint of the heart itself, but from the economic aspects, and perhaps especially from the viewpoint of the patient's morale and mental attitude. A final answer to this question can only be obtained by the controlled study of many hundreds of patients. However, something can be learned by the investigation of problems of allied nature in experimental animals, and it is with this approach to the problem that the present communication is concerned.

Method of Study. In order that a large enough series of animals might be employed so that the results would have statistical significance, rats were used in preference to larger animals. At first, attempts were made to ligate the coronary arteries but these were not successful. Consequently, the following technique was employed.

Under ether anesthesia the chest was opened by an incision through the left fourth interspace over the point of cardiac impulse. The ribs were quickly retracted by means of sutures previously placed around the rib above and the rib below the point of opening. The heart was pushed out through the incision by pressure on the chest. Three to five areas on the left ventricular surface near the apex were burned by the application of the head of a ten-penny nail heated almost to redness. The heart was then replaced and pressure exerted to expel as much air as possible from the chest. The incision was quickly closed by tying the sutures about the ribs. With practice it became possible to carry out the entire procedure from the time the chest was opened

until it was closed again within a period of about 30 seconds. The operative mortality at first was 60 to 70%, but with further practice this was reduced to 10 to 20%.

The rats surviving the operative procedure were divided into 2 equal groups, of which 1 was placed in small wire cages especially constructed so that they fitted fairly snugly around the rat. These small "straight-jacket" cages were constructed from "hardware cloth." It was found that for a 200-gm. rat a cage having an external diameter of 6 x 2 x 2 inches was of approximately the correct size, so as not to interfere with the animal's breathing, but at the same time to hamper markedly any movements. In the earliest experiments the animals which were to be later placed in these small cages were first trained by being put in them for a few hours on several successive days prior to the operation. However, later this practice was abandoned when it was found that the rats always tended to struggle somewhat for some few minutes when first put in the cages and then tended to remain rather quiet. Precautions were taken to see that the animals confined in these small cages had access to as much food and water as they desired.

The control animals were treated similarly except that they were put back into large stock rat cages, each of which held several rats. After periods of time varying from as short as 2 weeks in one experiment, to as long as 5 to 7 weeks in most of the experiments, the rats confined to the small cages—hereinafter to be called the "restricted rats"—were taken out and put in the usual stock cages. Notes were made daily concerning the general demeanor of the 2 groups of animals and their apparent clinical condition; autopsies were done on the animals that died.

In order to obtain quantitative data concerning the relative amount of activity of the restricted rats as compared to the control, another series of experiments was carried out and the activity was recorded by an apparatus similar to that devised by Tainter *et al.*[22] A wire cage large enough to hold 2 rats comfortably was suspended by a spring and 3 Harvard work adders were attached so as to record the motion of the cage in 3 different planes. An automatic record of the number of revolutions of the work adders was obtained by attaching to each one a string which wound around the axle of the recorder as it revolved. Thus, it was possible to measure the activity of the 2 animals in the suspended cage in terms of revolutions of the 3 work adders. With this apparatus the 2 rats could be left free in the suspended large cage or confined within the smaller "straight-jacket" cages placed within the larger suspended cage. Observations were made on normal rats and also on animals which had been subjected to cardiac injury, the latter rats being usually free in the large cage for 1 day, confined in the small cages for the 2nd day, and alternated in this fashion for a number of days. In this way it was possible to gain an idea as to how much confinement in the small cage did in fact restrict the activity of the rat.

In a 3rd series of experiments the rats were not confined but were allowed to choose their own activity by the use of the optional treadmill.* This apparatus consists of a small cage large enough to allow the rat to move around freely, but not large enough to allow space for much exercise. The cage is connected to a treadmill by a door which remains open. The number of revolutions of the treadmill are recorded on a small Veeder counter. The animals in this series of experiments were first made accustomed to the apparatus by being placed in it for a number of days prior to the chest operation. Following production of cardiac injury the animal was put back into the apparatus and the daily number of revolutions of the treadmill was noted.

In a 4th group of experiments the effect of forced exercise was studied. The heart was injured by burning in the usual way, and one or more days after this procedure one-half of the animals were forced to swim for varying periods of time. In order to separate the effects of exercise from those due to the wetting and chilling of the skin, the control animals were dipped in the water and

* This apparatus was obtained from the Geo. H. Wahmann Mfg. Co., Baltimore, Md.

taken out without being allowed to swim. The mortality and the rate of healing of the hearts in the control and the swimming animals were then compared.

Results. 1. *The Effect of Restriction of Activity on the Mortality Subsequent to Cardiac Injury.* In this series of experiments 142 rats were used. Of these, 46 died during or immediately after the operation

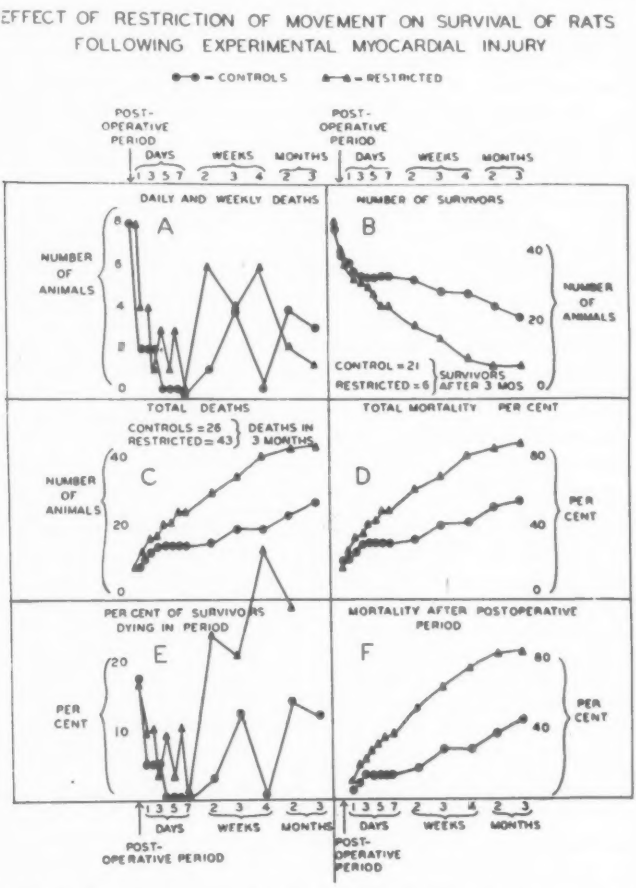

FIG. 1.—*A*, During the 1st month the number of deaths in the restricted animals (triangles) tended to be considerably greater than in the controls. The apparent decrease in mortality in the restricted animals during the 2nd and 3rd months is due to the small number of survivors in this group. *B*, *C*, *D*, *E*, These curves all emphasize the greater mortality in the restricted group. *F*, Elimination from consideration of the deaths occurring during the immediate postoperative period indicates that the difference in mortality due to restriction is really greater (*F*) than the difference in total mortality (*D*).

on the heart. The remaining 96 rats consisted of 47 controls and 49 restricted animals. The data concerning mortality and survival in these 2 groups are shown in Figure 1. The mortality in the postoperative period, which was arbitrarily taken as the time from the end of the operation until 9 o'clock the next morning, was the same in

the 2 groups, 8 animals dying in each during this period. In all subsequent periods the mortality was greater in the confined group, the difference being consistent and of rather striking degree. Thus, at the end of 3 months there were only 7 survivors out of the original 49 rats in the restricted group, and of these 7 survivors 5 were animals which had been removed from the "straight-jacket" cages 2 weeks after the operation. On the other hand, 21 of the 47 controls operated on survived the 3-month period. Similarly, the total number of animals dying in 3 months was 42 in the restricted group as compared to 26 in the controls. If the deaths during the postoperative periods are omitted from consideration, which would seem justifiable because such deaths were obviously related to the operative procedure rather than to the method of treatment, we are left with a total of 34 deaths in the restricted animals and 18 deaths in the controls.

Observations of the appearance of the 2 groups of rats were of some interest. Most of the animals in the control series who survived the first 2 days seemed to regain their strength and appetites rapidly, and these tended to assume the sleek and alert appearance of a normal rat. The restricted animals appeared unhappy, apathetic and asthenic. They tended to lose weight slightly, while the controls gained or remained constant.

The autopsy findings in these rats will not be discussed in the present communication, as these will form the subject of a separate report in which an attempt will be made to compare the rate of healing of wounds in the rat and in man, as well as the rate of healing of the hearts in the different animals with which this communication deals. Here it only need be stated that most of the deaths in the period immediately after operation were the result of hemorrhage from the heart, and that later deaths were due to infections in the thoracic cavity, pneumonia, cardiac rupture and, oftentimes, to unknown causes.

2. *The Total Daily Activity of Restricted and of Control Rats.* Observation of the rats confined in the small cages showed that from time to time they tended to struggle somewhat, but that this became less after the rats had been in the cages for a few days. The activity, as measured by the recorder, showed a very striking difference between animals confined in the small cages and those left free to wander at will in the larger cages (Fig. 2). The total number of revolutions of the work adder was usually 10 times as much in the case of the latter group. Thus, it is clear that the somewhat heroic straight-jacket method of producing restriction of muscular movement did in fact limit the activity, and to a very striking degree.

3. *The Spontaneous Activity of Rats Following Burning of the Heart.* In the experiments as previously described the rats have been artificially restricted in their movements and the animal had no opportunity to make a choice. Hence, it seemed desirable to carry out a group of experiments in which the animal would be free to exercise or not, as desired, and in which the amount of exercise carried out could be compared after the operation with that prior to it, in order to deter-

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mine how long a time elapsed before the rat tended to assume his pre-injury activity level.

The results of these experiments were rather surprising and are shown in Figure 3. Even following rather extensive searing of the ventricular surface each rat returned to his preoperative level of exercise in 3 to 7 days, the average being approximately 5 days. One is forced to

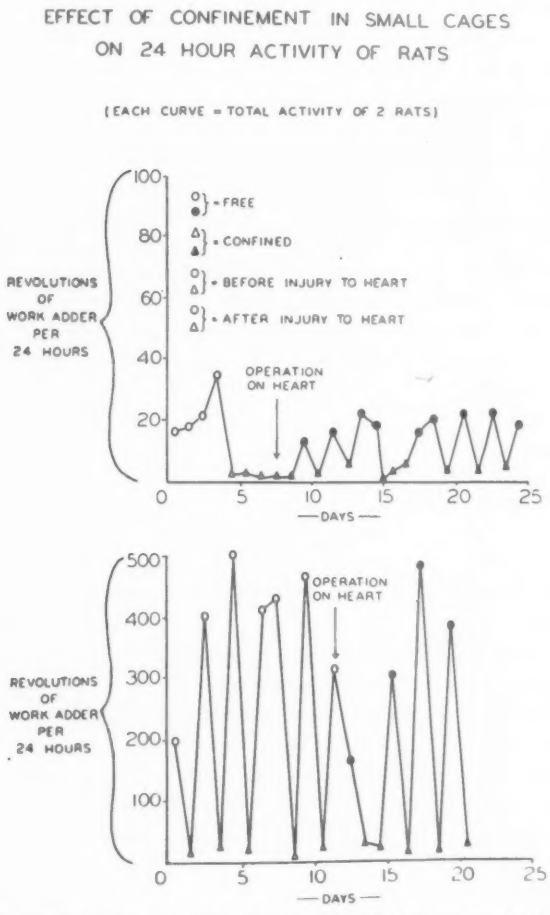

FIG. 2.—The results show that whether normal rats (hollow symbols) or rats with injured hearts (solid symbols) are employed, confinement in the small cages did result in well-marked decrease in the 24-hour activity. Although the method used is not entirely adequate for the purpose desired, the differences in activity, as measured, are so great as to seem well beyond any reasonable likelihood of error.

assume either that (1) the rat deliberately undertakes a level of activity which is physically harmful; or (2) that such early resumption of normal activity is not harmful. In order to attempt to distinguish between these 2 alternatives, additional experiments were done.

4. *Effect of Strenuous Exercise on the Mortality Following Myocardial Injury.* (See Table 2.) They would seem to indicate that strenuous

exercise is perhaps harmful when begun within the first 48 hours after injury to the heart. However, after that period of time there is little difference in the mortality in the 2 groups. Some of the early deaths were unexplained at autopsy and may have been the result of ventricular fibrillation. An analysis of the deaths caused by cardiac rupture

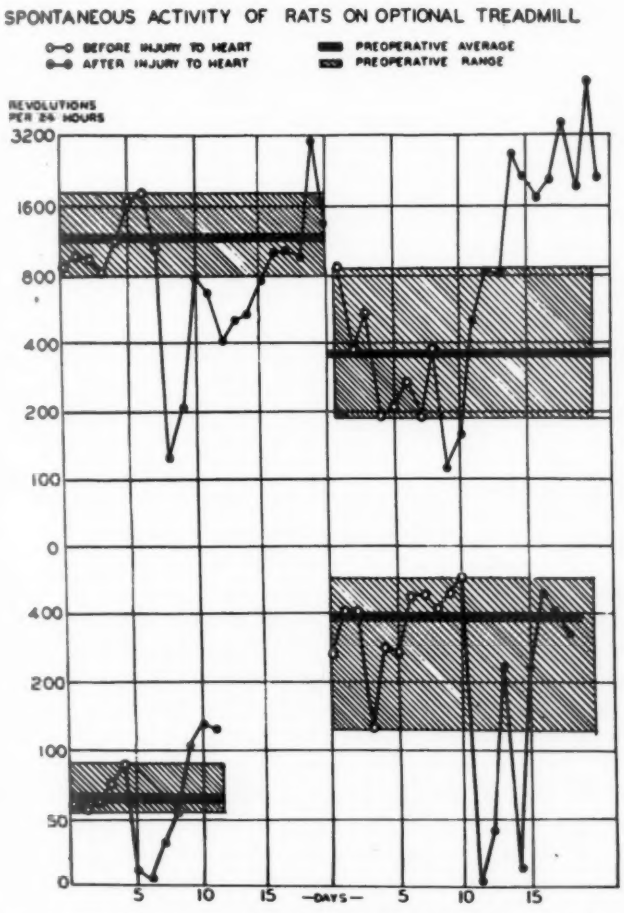

FIG. 3.—No compulsion was employed, the animals being free to follow their own desires both in the preoperative and postoperative periods. Two points are of interest: (*a*) No rat chose to avoid exercise entirely, even on the 1st postoperative day. (*b*) The general tendency was toward a marked reduction in exercise during the 1st 48 hours after cardiac injury with a return to (or above) the preoperative level of activity within 3 to 7 days.

is interesting. The period of time from the 5th to the 15th postoperative day was found to be the optimum period of development. None of the animals suffered this accident while in the act of swimming or within 6 hours following cessation of the exercise. Rupture occurred later in the animals forced to exercise than in those which were not exercised. The importance of factors other than exercise *per se* is

emphasized by the study. Further investigation of these problems is being carried out.

TABLE 2.—THE EFFECT OF SWIMMING ON THE MORTALITY OF RATS WITH MYOCARDIAL DAMAGE
(The letters indicate a death occurring on that day)

		Postoperative day														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Controls (11 rats)	No swimming			I							R						
Exercised	Amount of exercise: 10 minutes 3 times a day																
Group 1 (10 rats)	Begun 1st postoperative day and continued *every* day thereafter	U	I				I										
Group 2 (11 rats)	Begun 3rd postoperative day and continued every *other* day thereafter			U										•		R	
Group 3 (10 rats)	Begun 5th postoperative day and continued every *3rd* day thereafter				I				R							R	

Key to letters:
I indicates death due to infection.
U indicates that no cause of death was found at autopsy.
R indicates that death was due to cardiac rupture.
Note: At the end of 45 days of the experiment no more deaths had occurred.

Discussion. The data which are presented seem to have established the following points: (1) Under the conditions of these experiments, immobilization of the animals caused a pronounced increase in the mortality following injury to the myocardium. (2) Such immobilization was accompanied by a well-marked restriction of activity. (3) When the animals were allowed to follow their own desires they deliberately chose to resume a normal life—as regards physical exercise—within less than a week after the cardiac injury. (4) When rats had been allowed to rest for as short a time as 3 days following severe injury to the heart, the mortality was not significantly increased by having them carry out strenuous exercise for 10 minutes 3 times a day. In view of these findings it seems justifiable to conclude that—in the case of the rat at least—prolonged restriction of activity following cardiac injury is not only not beneficial, but actually harmful.

There are a number of reasons why one is not justified in drawing any direct conclusions concerning patients from these experiments. First of all there is the species difference. In the second place, the type of injury induced is artificial and does not bear close resemblance to that occurring in disease, even in a condition such as myocardial infarction which is likewise accompanied by focal injury to the heart. Third, the rats were young and in excellent health prior to the cardiac injury, a condition which obtains only in a minority of the patients with myocardial infarction. Fourth, the rate of the healing process

in the heart of the rat is probably much faster than in that of man. Finally, the artificial conditions of restricted activity in the animals do not bear a close resemblance to rest in bed of patients, but are more analogous to the use of a straight-jacket. Granting the validity of these points of dissimilarity between the experimental results presented in this communication and myocardial infarction in man, the data would seem to us at least to justify an attitude of skepticism con-

TABLE 3.—THEORETICAL EFFECTS OF REST IN BED ON FATAL COMPLICATIONS OF MYOCARDIAL INFARCTION

Complication	Probable effect of prolonged bed rest on the likelihood of its occurrence	Remarks
Ventricular fibrillation	Decrease	Quinidine perhaps more important than absolute rest; no evidence concerning optional position
Rupture of heart	Decrease	These complications are very rare after the end of 2nd week; recumbent posture tends to prevent
Acute circulatory collapse	Decrease	
Renal insufficiency	Decrease	
Systemic embolism	Decrease	May occur many months later
Ventricular aneurysm	Decrease	No evidence concerning optional position
Further myocardial infarction	Increase	Both spread of original thrombus and formation of new ones favored by prolonged rest
Pulmonary edema	Increase	Sitting position tends to prevent
Pulmonary embolism	Increase	Failure to move legs favors thrombosis in veins
Pneumonia	Increase	Elderly subjects confined to bed from any cause tend to develop these complications
Cerebral thrombosis	Increase	
Prostatic obstruction	Increase	

Note that those complications which tend to be prevented by absolute rest usually occur within the first 2 weeks—while the complications which are favored by bed rest tend to occur later.

TABLE 4.—THEORETICAL EFFECTS OF PROLONGED REST IN BED ON SUBSEQUENT MORBIDITY OF PATIENTS SURVIVING MYOCARDIAL INFARCTION

Complication	Probable effect of prolonged bed rest on the likelihood of its occurrence	Remarks
Angina pectoris	Uncertain	Anginal attacks are more frequent in recumbent than in sitting position
Congestive failure	Uncertain	Recumbency aggravates congestive failure when present
Further myocardial infarction	Increase	Mild activity increases coronary flow and probably tends to prevent thrombosis
Cardiac neurosis	Increase	The longer the period of absolute rest the greater the psychic trauma

cerning the desirability of prolonged and extreme bed rest in patients. It therefore seems worth while to consider certain theoretical aspects of this question.

The various complications which are the common causes of death in patients with myocardial infarction, as well as those which are likely to occur subsequently in patients who survive this disorder, are summarized in Tables 3 and 4 and the probable effect of prolonged rest in bed as the likelihood of their occurrence is indicated. It seems probable that ventricular fibrillation, rupture of the heart, acute circulatory collapse and renal insufficiency due to diminished blood pressure are less likely to develop if the patient is kept rigidly in bed in the recumbent position. However, it should be noted that these complications tend to occur in the first 2 weeks and are rare after this time.

It seems probable that prolonged rest would tend to prevent the development of ventricular aneurysm. Whether this complication would tend to develop more readily in the sitting than in the recumbent portion position is uncertain. In most patients the blood pressure is somewhat higher sitting, but all who have studied the subject agree that the cardiac output is 5 to 20% greater in the recumbent than in the sitting position. The work of the heart per minute might therefore be greater in the one position in some patients and in the other position in other patients. Since the pulse rate is somewhat faster in the sitting position, it is probable that the work per beat, and hence the amount of energy developed at each contraction, is greater in the recumbent posture. From this point of view one might expect that the development of ventricular aneurysm would be more likely to occur in a recumbent than in a sitting patient, both of whom were remaining at rest in bed.

As regards peripheral embolism resulting from ventricular mural thrombosis, the studies of Mallory, White and Salcedo-Salgar[19] make it seem probable that this complication would be most likely to occur in the first 2 weeks. They found that mural thrombosis often begins early and that the thrombus is frequently completely organized by the 16th day. However, they found in other subjects that thrombosis might occur weeks or even months following the infarction. Since it seems probable that a patient walking around out of bed would be more likely to produce an embolus than a person remaining quietly in bed, it would seem that for the purpose of the prevention of this complication a period of bed rest lasting several months would be indicated. The question arises, however, whether in view of the relative rarity of this complication one would be justified in keeping all patients in bed for such a prolonged period in order to prevent embolism in an occasional patient. Since, as will be pointed out in succeeding paragraphs, prolonged rest in bed has a number of important disadvantages, it would not seem, on the basis of theoretical considerations, that such a plan of treatment is desirable. In some patients, and perhaps in the majority, the development of mural thrombosis leads to certain manifestations, including slight fever, a

persistent leukocytosis and sustained increase in the sedimentation rate. One might therefore take the position that in cases who still display these abnormalities at the end of a 2- to 3-week period a longer period of rest in bed is indicated than in the usual instance.

There is a series of important complications of myocardial infarction which are likely to develop late, that is, after the first 2 or 3 weeks. These include additional infarction as the result either of formation of new clots in a different vessel, or the spread of the original clot, acute pulmonary edema, pulmonary embolism from silent thrombi in the vessels of the legs, bronchopneumonia, cerebral thrombosis and difficulty in urination which may at times progress to anuria. On theoretical grounds one would expect these complications to develop more readily in persons remaining recumbent in bed than in individuals who are either allowed to sit up in bed, or perhaps, better, allowed to sit in a chair and walk around a slight amount each day. Without having statistics to strengthen the opinion, I have the impression that this second group of complications causes more deaths in patients with coronary thrombosis than does the first group of conditions, which usually occur early and which probably are less apt to occur in patients kept in bed in the recumbent posture. On theoretical grounds, then, one can logically take the position that, generally speaking, a patient with myocardial infarctions should be kept in bed for a period of 2 to 3 weeks, being allowed to sit up in bed the 3rd week, and after that being allowed out of bed for very slowly increasing periods of time. The desirability of such a plan of management is far from established on the basis of available evidence. However, it seems reasonable, in the light of the considerations which have been mentioned.

When we turn from those conditions which tend to cause death during the initial illness to the conditions which are apt to occur as late complications in individuals who have recovered from the acute myocardial infarction, we likewise encounter further uncertainty concerning the desirability of prolonged rest in bed. Whether a patient who is kept strictly in bed for only 2 weeks following myocardial infarction is more apt or less apt to have angina pectoris in the future than a similar patient who has been in bed for 3 months is uncertain. In favor of prolonged bed rest is the fact that it should theoretically allow more time for the uninjured muscle to take on an additional load. Even a slight increase in the oxygen requirement of the heart might tend to induce angina in a patient where the balance between oxygen need and oxygen supply was finely adjusted. On the other hand there is considerable evidence that exercise in moderation tends to benefit patients with angina pectoris. Thus, Heberden[11] cited a patient who was nearly cured following several months during which he undertook the task of sawing wood for ½ hour daily. Connor[4] likewise has emphasized the value of exercise in patients with angina pectoris, and we have believed for a long time that those individuals with this disorder who remained moderately active (but below the pain threshold) were more apt to improve than the patients who restricted their activities to an absolute minimum. Probably, physical activity with a slight

increase in the metabolism of the heart tends to increase the collateral circulation through the healthy coronary branches. In any case it is worth emphasizing that patients who are at rest are much more apt to have anginal attacks in the recumbent than in the sitting posture,[10] and hence that from the standpoint of preventing the anginal attacks a patient who is to be subjected to prolonged bed rest should be allowed to be in the sitting posture several hours a day, at least after the first 2 or 3 weeks following infarction.

As regards congestive heart failure, which is the ultimate cause of death a in large percentage of the people who have had myocardial infarction, it is well known that the upright position favors the development of edema in the legs, while the recumbent position favors the development of edema in the lungs. Since the latter is more serious than the former it would seem again that there is an advantage in having the patient sit up rather than lie down in bed.

The likelihood of the development of additional myocardial infarction has already been discussed, and here again it seems probable that a moderate amount of activity, with the attendant increase in coronary flow, would tend to prevent the formation of thrombi in the vessels.

One of the most common complications of myocardial infarction is cardiac neurosis. Every experienced physician has seen many patients in whom the disability due to the patient's anxiety and fright causes far more suffering than the actual cardiac disease itself. The longer a patient is forced to stay in bed and the more he is impressed with the dire consequences which may follow the premature resumption of activity, the more likely he is to develop a cardiac neurosis. This point is not an inconsequential one because it is just as important for the physician to prevent mental suffering as to prolong physical life. The theoretical disadvantages of strict rest in bed in the recumbent position can be overcome in large measure by allowing a patient to sit up in a chair several hours a day and perhaps to walk a few steps in a gradually increasing regimen. We know of no evidence which is contrary to the idea that the activity of patients should be restricted for many weeks following infarction. The question is not whether restriction of activity is desirable but rather whether *prolonged rigid* restriction is desirable.

A strict régime of rest in bed has 2 components. One of these is decrease in the metabolic rate of the body and presumably of the heart as well; the other is muscular immobilization. It is the latter which has been studied in the present communication and the data show very clearly that such immobilization is quite harmful. In the case of the rats confined to the "straight-jacket" cages the degree of immobilization is greater than in the case of the patient kept rigidly in bed, and perhaps the degree of metabolic reduction is less. Under the conditions in which our experiments were carried out it is clear that any advantages resulting from decreased metabolic rate were far outweighed by the harmful effects of muscular immobilization. Whether or not this is true in patients with acute myocardial injury is unknown. If one makes the reasonable assumption that decrease in metabolism is

desirable in such patients, there are still no accurate data on the question of how this objective may best be achieved. The patient who is not dyspneic presumably has a lower metabolic rate lying down than sitting up. However, in the patient with even a mild degree of orthopnea the reverse is probably true. Data are needed concerning the relation of defecation to this problem. The respective metabolic increments induced by using a bed pan and a bedside commode should be investigated. Similarly, observations concerning the oxygen consumption during unhappy recumbency *versus* satisfied sitting are desirable. Until information of this type is available it is well for us to bear in mind that prolonged bed rest following myocardial infarction has serious psychic disadvantages. The physical advantage to a patient of rest in bed for a period longer than 2 weeks is as yet unproven. The available evidence derived from morbid anatomy would suggest that rigid rest for a period of 1 month to 6 weeks may be desirable. The evidence obtained from experiment would perhaps suggests that confinement in bed for a period this long is undesirable. A final answer can only be derived from a critical and careful study of many hundreds of patients. Until such a study has been carried out, we would maintain an open mind about the question, realizing that while there are advantages there are also disadvantages in keeping a patient rigidly in bed for a prolonged period.

Summary. Following experimental injury to the hearts of rats the mortality is decidedly greater when the animals are kept closely confined in small cages which restrict muscular activity.

Animals so confined display considerably less activity, as measured by the work adder method, than control animals allowed to wander freely about in larger cages.

Observations with the optional treadmill have shown that following injury to the heart the rat tends to return to the preoperative level of exercise within a period of 3 to 7 days.

Enforced strenuous muscular effort even when carried out within 24 hours after cardiac injury, did not materially increase the mortality in rats. Likewise, such exercise carried out 3 or more days after the operation did not cause a significant increase in mortality.

The question of the desirability of prolonged and rigid rest in bed following myocardial infarction in patients has been discussed and it has been pointed out that this procedure has serious disadvantages as well as some advantages. On the basis of the available evidence it would appear that during the first 2 weeks the advantages of strict bed rest probably outweigh the disadvantages, but that after this time the reverse is probably true.

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ALLOXAN DIABETES IN THE RABBIT

A CONSIDERATION OF THE MORPHOLOGIC AND PHYSIOLOGIC CHANGES

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THE production of diabetes in experimental animals by the injection of alloxan has evoked general interest and discussion. This drug has a specific effect on the pancreatic islets of Langerhans and thereby produces diabetes within 24 hours. The relation, if any, between alloxan diabetes and human diabetes immediately presents itself and this question is being intensively studied at the present time.

That alloxan, when injected intravenously into rabbits, may produce a fatal hypoglycemia was first recorded by Jacobs[15] in 1937. Since

only the gross pathology was studied, the islet changes were not recognized. Dunn, Sheehan and McLetchie[6] were the first to stimulate widespread interest in alloxan when they reported a selective necrosis of the islets of Langerhans following intravenous injection into rabbits. The majority of these animals "died during the 1st day or so with distinctive symptoms, which were not referable to renal disease." In several animals they noticed a low blood sugar shortly before death.

Bailey and Bailey,[1] reviewing these data, considered the hypothesis that with destruction of the islet cells there might be a massive release of insulin. Hence these animals could be dying in hypoglycemia. Further, if hypoglycemic death could be prevented, then with extensive destruction of the islets the animals should develop diabetes. Support for this hypothesis was gained by the fact that hypoglycemic death was prevented by the repeated administration of intravenous dextrose, and diabetic animals were obtained within 24 hours.

Brunschwig, Allen, Goldner and Gomori[3] report "sustained hyperglycemia" in 5 dogs observed for 2 to 3 weeks, and "transitory hyperglycemia" in rabbits following alloxan. Three human patients with carcinomatosis, one arising in the islets of Langerhans, were also given alloxan intravenously but no immediate effect was obtained. Later Brunschwig, Allen, Owens and Thornton* gave a subsequent report upon the patient with carcinomatosis arising in the islets of Langerhans and stated that temporary symptomatic relief from hypoglycemic attacks for brief periods of 10 to 20 days, followed each series of alloxan injections.

Dunn, Kirkpatrick, McLetchie and Telfer[4] discussed in detail the pathologic findings in the rabbits and reported permanent hyperglycemia with similar pancreatic lesions in the rat following alloxan. They described a ring of intact cells at the periphery of the islets and suggested that these might be alpha cells. Dunn and McLetchie,[5] in describing alloxan diabetes in the rat, emphasized the fact that in this animal the kidneys were also not infrequently damaged. Diabetic acidosis and coma in the rat have also been observed.

The dog with alloxan diabetes was first carefully studied by Goldner and Gomori[8] who noticed a remarkable specificity of the dosage. Single doses exceeding 100 mg. per kg. caused death within a few hours. A dose between 75 and 100 mg. per kg. produced a diabetic uremic syndrome with death within 1 week. A dose of 50 to 75 mg. per kg. produced typical diabetes without renal lesion. Doses of 25 mg. per kg. were without effect. Guinea pigs, cats and pigeons were likewise given alloxan but without the production of permanent diabetes. By differential stains they showed that on the 3rd day after injection only alpha and non-granular cells remained.

Studying the rat, Gomori and Goldner[12] found nuclear pyknosis of the beta cells 3 hours after the injection of alloxan. Hooded rats, they found, were resistant to this drug. Hughes, Ware and Young,[14] however, report changes in the beta cells 5 minutes after the subcu-

* Brunschwig, A., Allen, J. G., Owens, F. M., Jr., and Thornton, T. F.: J. Am. Med. Assn., **124**, 212, 1944.

taneous injection of alloxan into rats. They were able to reproduce in the rabbit the hyperglycemia-hypoglycemic blood sugar curve that follows alloxan by injecting adrenalin and simultaneously the amount of insulin, as protamine zinc insulin, that would normally be present in the rabbit pancreas.

Goldner and Gomori[9] showed that the initial hyperglycemia following alloxan can be prevented with insulin and the subsequent hypoglycemia by dextrose injection; yet the beta cells will degenerate and diabetes develop.

Bailey, Bailey and Leech[2] found that diabetic cataracts developed within 1 to 3 months in rabbits and rats kept alive with alloxan diabetes. Small repeated injections were tried, and whereas 20 mg. per kg. have failed to produce diabetes when given 3 times a week for 2 months, a larger dose of 40 mg. per kg. daily produced diabetes after 8 and 14 injections respectively. In the 2 rabbits with the larger dosage, certain islet cells presented a clear-cut picture of hydropic degeneration. Mitosis was also seen in several cells. In the islets some changes were reversible and some irreversible. They found 200 mg. per kg. subcutaneously the most effective dose for the rat, as 15 of 18 rats given this dose developed diabetes.

Hard and Carr[13] emphasize cytoplasmic vacuolation in the adrenal medulla in addition to destruction of the islets of Langerhans in the rabbit made diabetic with alloxan.

Goldner and Gomori[10] recently showed that destruction of the adrenal medulla prior to alloxan injection prevented the initial hyperglycemic phase and that animals who had been made diabetic with alloxan or pancreatectomy failed to develop marked hypoglycemia after alloxan injection. Furthermore, insulin assay of the pancreas from 3 dogs made diabetic with alloxan showed only 0.5 unit per gm. as compared with the normal of 2 to 3 units per gm. of pancreas.

Thorogood[18] injected 50 rats subcutaneously with 200 mg. per kg. of alloxan. Ten developed diabetes, 10 were not affected and 30 died.

A detailed summary of the literature can be found in a recent Diabetic Progress article by Joslin.[16]

The purpose of this paper is: (1) to correlate and report in detail the pathologic findings in the pancreas and other organs of the rabbit at varying intervals after the intravenous injection of 200 mg. per kg. of alloxan; (2) to discuss the diabetic complications which have occurred in this animal, as well as those looked for but not found; and (3) to discuss the physiology of the blood sugar changes following the injection of alloxan.

Since the blood sugar values uniformly pass through 3 stages—transitory hyperglycemia, transitory hypoglycemia and permanent hyperglycemia—a study has been carried out to determine at what time the cells of the islets of Langerhans first show morphologic changes, whether the alterations seen microscopically are the same or different in each stage, and whether processes in the islet cells seem to represent a continuous effect. For these studies the rabbit has been used as the experimental animal. In spite of its numerous shortcom-

ings as a test species in the laboratory, the ease of intravenous injection, the possibility of repeated blood chemistry determinations and the facility with which alloxan diabetes is produced have recommended it for these experiments.

Materials and Methods. All rabbits used in these experiments have been either Dutch or Chinchilla strains.

In the early experiments a 2% aqueous solution of alloxan was given intravenously in 3 separate injections at 15 minute intervals for the production of diabetes. Later a single injection of a 5% aqueous solution of alloxan was used with equivalent results. The total diabetogenic dosage was 200 mg. of alloxan per kg. of body weight. Smaller doses, as specified below, were used for the production of transitory diabetes. Only freshly prepared solutions were used. The alloxan used was kindly supplied by the American Cyanamide Company.

Blood sugars were taken from the ear vein by the capillary method and determined by the micro procedure of Folin and Malmos.[7] Smith's[17] modification of Benedict's method was used for the determination of the percentage of glycosuria.

The diet throughout the investigation consisted of rabbit pellets which contain carbohydrate 63%, protein 13%, fat 3% and fiber 12%. These pellets contained adequate vitamins and minerals.

On the day of injection the rabbits, which had been fasted overnight, first had 2 control blood sugar samples taken. Immediately afterward, the alloxan was injected slowly. Blood sugar samples were thereafter taken at 15 minute intervals for the 1st hour and 30 minute intervals thereafter until a convulsion occurred. The hypoglycemic convulsion was relieved with 2 cc. of 50% dextrose intravenously, and thereafter the rabbits were allowed to eat. This prevented further convulsions. Every rabbit given alloxan in this way was diabetic within 36 hours.

In nearly all cases insulin was begun on the 3d day, since by this time the blood sugar level usually approached 400 mg. and frequently diacetic acid had appeared in the urine.

The animals were sacrificed, usually by air embolism, at various intervals, as indicated in the discussion of the results. Autopsies were performed immediately, the pancreas being the first organ removed. Routine fixation was in Zenker's fluid with phloxine and methylene blue staining of the sections. For studies of the granules of the islet cells, blocks of pancreatic tissue were fixed in Bouin's fluid and sections stained with Gomori's method for these structures.[11]

The Islets in the Phase of Initial Hyperglycemia. For the study of the pancreas in this phase, material of 2 types was prepared. The first of these consisted of 3 rabbits, each given 200 mg. per kg. of alloxan in a single injection administered over a period of 10 minutes. One was sacrificed ½ hour after the end of the injection, 1 after 1 hour, and 1 after 2 hours. The phloxine and methylene blue stain was used. For study of other intervals and of the rôle played by the different types of islet cells, 3 rabbits were anesthetized with nembutal, ½ gr. per kg. subcutaneously 1 hour preoperatively, and sufficient nembutal intravenously immediately before operation to produce surgical anesthesia. Less than ¼ gr. per kg. was required. The abdomens were opened and a biopsy of the normal pancreas taken. Alloxan, 200 mg. per kg., was then injected intravenously in 10 minutes. Successive biopsies were taken as follows:

Rabbit No. 1. Normal, 15 minutes, 30 minutes, 1, 2, 4 and 6 hours after the end of the injection.

Rabbit No. 2. Normal, 10, 15, 30, 45 and 60 minutes after the end of the injection.

Rabbit No. 3. Normal, 5, 15, 30 and 60 minutes after the end of the injection.

The specimens were fixed in Bouin's solution and stained with Gomori's granule stain.[11] The specimens of the pancreas removed before the injection of alloxan corresponded to published descriptions.[11]

In the specimen secured 5 minutes after the injection of alloxan, the nuclear membranes of many islet cells, especially the beta cells, were more prominent and their cytoplasm was rather clear with some loss of granules. These changes, though slight, were definite and indicate the speed of localization of alloxan in the islet cells.

At 10 and 15 minutes, the alpha cells appeared normal but most of the granules had disappeared from the cytoplasm of the cells at the centers of the islets. The nuclei were essentially the same as at 5 minutes.

At 30 and 45 minutes the central cells were somewhat more closely packed than in previous specimens, their nuclei were more shrunken, but the chromatin was still granular. The cytoplasm of these cells was still intact in outline but there was further loss of granules. Numerous normal alpha cells were seen.

In specimens at 1 hour and 1½ hours, the nuclei of the central cells were further shrunken and the chromatin formed a compact deeply staining mass. Their cytoplasm had become less dense and early cytoplasmic disintegration was apparent in some areas. The capillaries were congested.

At 2 hours, these processes had extended further, and distortion of the general architecture of the islets was more clearly indicated than at shorter intervals after the administration of alloxan.

These findings indicate that degenerative changes begin in the islet cells very quickly after the injection of alloxan and progress steadily toward the fully established lesion associated with diabetes. At no stage was neutrophil infiltration seen and the stroma, blood-vessel walls and pancreatic parenchyma remained unchanged.

The Islets in the Phase of Hypoglycemia. Four rabbits were sacrificed during the phase of hypoglycemia (at 3, 4, 5 and 6 hours after the end of the injection). There were also available 2 biopsy specimens from Rabbit No. 1, described above.

Three hours after the end of the injection of alloxan, the islet cells showed a somewhat further progression of the processes described in the preceding section. The islets were somewhat swollen. The nuclei of the majority of the islet cells were pyknotic, being composed of homogeneous masses of very deeply staining chromatin. The cytoplasm was irregular in outline and took the phloxine stain strongly. The cells displaying these changes were separated somewhat from one another. Certain other cells located largely at the periphery of the islets were very well preserved. These appeared to be alpha and non-granular cells, no normal beta cells being encountered. No infil-

tration with polymorphonuclear leukocytes or wandering cells was seen. The blood-vessels, stroma and acinar tissue were normal.

In the rabbit sacrified 4 hours after injection and in the biopsy at 4 hours (as described in the previous section) there was further progression of the changes in the islets of Langerhans. The cells with pyknotic nuclei and degenerating cytoplasm had coalesced somewhat, so that the individual islets were smaller than at 3 hours. The number and distribution of cells which had not undergone degeneration was unchanged.

At 5 hours after injection and in the biopsy 6 hours after alloxan administration, the coalescence of the islet cells had progressed further and the number of degenerated cells in each islet was smaller. This was interpreted as an indication that some of them had disintegrated completely. By the end of 6 hours, more of the affected cells had disappeared without infiltration of polymorphonuclear leukocytes or wandering cells. The number, character and distribution of the morphologically normal cells were the same as in rabbits sacrificed at shorter times.

The lesions in the period of hypoglycemia, then, were regarded as a progression of changes which began very quickly after the injection of alloxan. There was no alteration in the character of the lesion which could be correlated with the rapid drop in blood sugar. At the height of the period of hypoglycemia, the lesion was approaching that which was found in the diabetic phase.

The Islets in the Phase of Diabetes. Fifteen rabbits were studied histologically in the phase of diabetes. Two of these were sacrificed 1 day after injection, 4 at 3 days, 1 at 4 days, 3 at 12 days, 1 at 14 days, 1 at 20 days, 1 at 3 months, 1 at 5 months and 1 at 5½ months. There was also available material from 1 rabbit whose pancreas was biopsied at 3 days and again at 84 days after the injection of alloxan.

In the rabbits sacrificed within 3 weeks after the onset of diabetes, the remnants of the islets were very inconspicuous. Compared with the normal islet of Langerhans in a control rabbit (Fig. 1) the islet 3 days after the injection and 2 days after the onset of diabetes showed that all the degenerating cells had disappeared, whereas the cells unaffected by the alloxan retained their previous morphology (Fig. 2). The islet was somewhat collapsed and flattened. In the central portion the stroma cells remained intact and no inflammatory cell infiltration was noted. It is likely that some islets had disappeared entirely, for they seemed to be less numerous than in control sections, and occasional small mats of fibrous tissue in the usual position of islets were interpreted as islets of which only the stroma remained. Thus, the lesion of fully developed alloxan diabetes could be characterized as a loss of all beta cells with persistence of small numbers of alpha and nongranular cells in the absence of detectable injury to the external secreting tissue of the pancreas.

The rabbits sacrificed 2, 2½, 5 and 5½ months after injection had remained diabetic. They had been maintained in good general condition by the administration of adequate doses of insulin. All had,

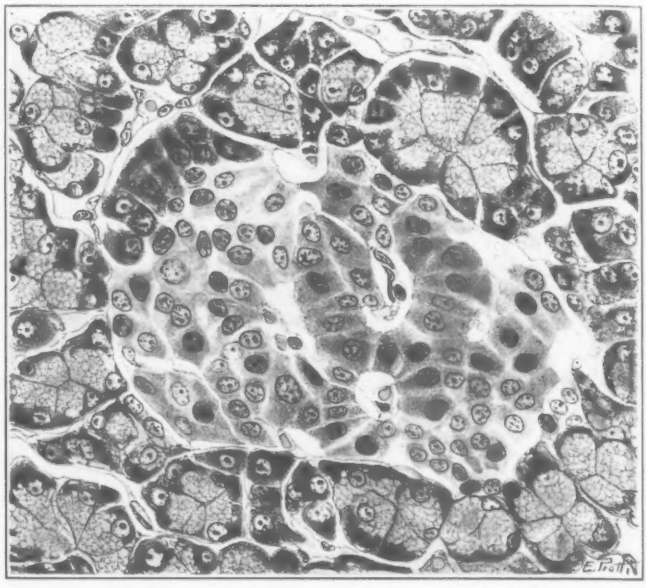

FIG. 1.—Islet of Langerhans in the pancreas of a control rabbit. (Camera lucida × 1300, reduced.)

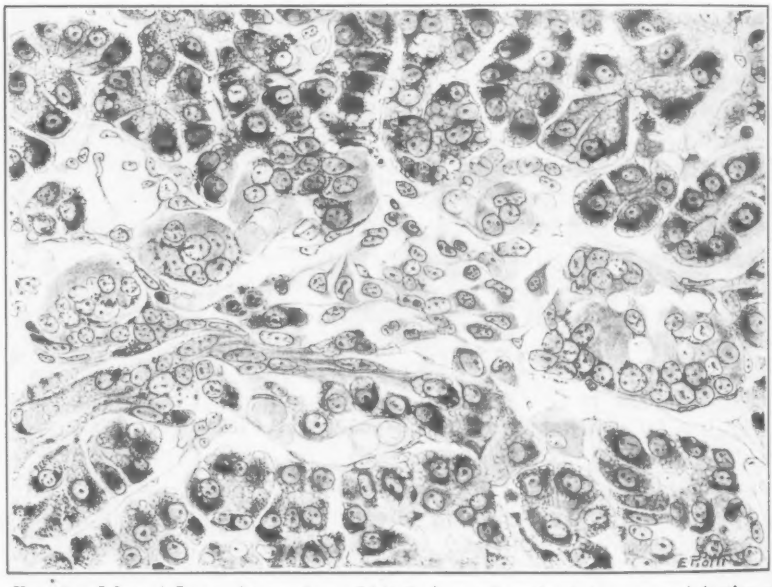

FIG. 2.—Islet of Langerhans of a rabbit 3 days after the intravenous injection of alloxan. The rabbit had well-established diabetes. The functional cells at the center of the islet, including all the beta cells, are destroyed, though the stromal cells persist. There is no inflammatory cell infiltration. The few preserved functional cells at the periphery are alpha and agranular cells. (Camera lucida × 1300, reduced.)

however, developed cataract. In this period there was one biopsy at 84 days after injection.

The findings in the pancreas in the animals allowed to survive for several months after the establishment of diabetes by means of alloxan was confined to the islets. The total number of islets was small, suggesting that some of them had disappeared without leaving any trace. Those which survived were composed of masses of cells resembling alpha cells as far as could be judged by phloxine and methylene blue stain (Fig. 3). The pancreas of 1 rabbit sacrificed at 3 months, and the biopsy material were stained by Gomori's method. In these 2 specimens, the cells were wholly alpha cells and confirmed the impression obtained from histologic sections prepared by routine methods. No beta cells could be identified. The number of cells in these islets was greater than the number surviving at 3 days after the injection of alloxan. It appeared probable, therefore, that there was some proliferation of the alpha cells, though no mitoses were seen in any of the rabbits receiving 200 mg. per kg. of alloxan.

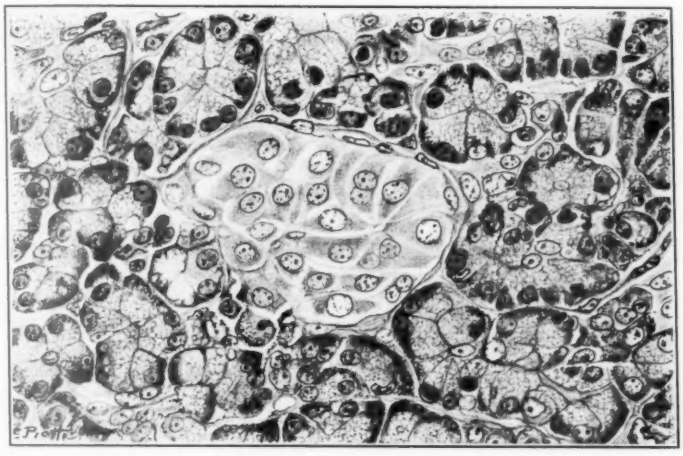

FIG. 3.—Islet of Langerhans of a rabbit 2 months after the intravenous injection of alloxan. Diabetes was present 24 hours after the injection and persisted to the time of sacrifice. The islet consists of a group of alpha cells without any beta cells. (Camera lucida × 1300, reduced.)

The Islets in Diabetes Induced by Small Doses. As pointed out in a previous publication,[2] the repeated injection of 40 mg. of alloxan per kg. in rabbits over a period of 2 to 3 weeks induced a gradual rise of the blood sugar. After the injections were stopped, the blood sugar fell toward normal, indicating that the lesions were reversible from the physiologic point of view. We now have 3 rabbits which were sacrificed after the second blood sugar value of 200 gm. per 100 cc. was obtained. The lesion in the islets of Langerhans differed in many respects from that induced by large single doses of alloxan. Many types of alteration were encountered in the cells. Some of them

appeared entirely normal. Others had lost their specific granules; still others showed a few small vacuoles. In some, there was typical hydropic degeneration similar to that described in pituitary diabetes. Occasional cells displayed irreversible changes, as judged by loss of the nucleus. Scattered mitoses were encountered, but in no instance more than 1 per islet (Fig. 4). Many islets showed no mitoses. In none of the sections was there inflammatory cellular infiltration.

This type of alteration in the islet cell of the pancreas was striking and it would be difficult to match it among the well-recognized lesions of islet cells. It suggests that different cells receive various degrees of injury by the small doses of alloxan. From the standpoint of morphology of the individual cells, some of these changes are reversible, while others are irreversible, the former predominating. There is some

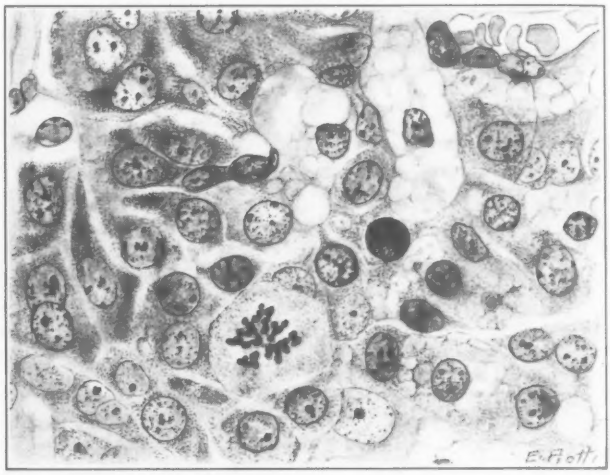

FIG. 4.—A portion of an islet of Langerhans of a rabbit developing mild diabetes after repeated injections of alloxan, 40 mg. per kg. The cells show a variety of changes. Some are essentially normal. Others show various degrees of hydroptic degeneration. One is in mitosis. (Camera lucida × 1300, reduced.)

replacement of irreversibly altered cells, as indicated by the mitoses. This is in conformity with the observation that the diabetes is physiologically reversible. In these islets, there was no scar formation and no inflammatory cellular infiltration. The acinar tissue appeared entirely normal.

Changes in Organs Other Than the Pancreas. The changes in organs other than the pancreas appear to be minimal. Our findings are in conformity with those which have been published elsewhere.[4,6, etc.] In the rabbits sacrificed within 3 days after the injection of 200 mg. per kg. of alloxan the kidneys showed a mild degeneration of the tubular epithelium. This consisted of vacuolization and some desquamation of the cells. The glomeruli appeared essentially normal. In rabbits sacrificed at longer periods after injection, there were no lesions which could be definitely correlated with the administration of alloxan,

though the rabbit is a poor experimental animal for the exact interpretation of minor renal lesions. The slight evidence of morphologic change in the kidney correlates well with the absence of changes in nonprotein nitrogen of the blood.

In rabbits sacrificed within 3 days after the injection of alloxan, some of the liver cord cells showed mild fatty metamorphosis, but no massive necroses were seen. The livers of rabbits sacrificed from 2 to 5 months after injection appeared entirely normal.

Sections of all the endocrine glands were studied in each of the animals. These studies included the pituitary. All these tissues, with the exception of the pancreas, appeared within the range of normal. There was some congestion of the vessels in and about the adrenal in the animals sacrificed within the first 24 hours. This change did not seem sufficiently constant or striking to permit the statement that it was beyond the possible range of normal animals sacrificed in the same way. While evidence has been published that the adrenal gland plays a rôle in the physiologic changes,[10] we find it difficult to regard any morphologic alteration which we have seen as a reflection of this activity.

Histologic sections of other organs showed no lesions due to the injection of alloxan.

Diabetic Complications. It has been shown elsewhere[1,2] that diabetic coma results in certain animals—both rats and rabbits—unless the diabetes produced by alloxan is controlled by the administration of insulin. We did not find any histologic changes which were to be correlated with the development of diabetic coma in these animals, although exhaustive cytologic studies of the brain were not undertaken. The technique of alloxan diabetes, however, could be well used in making such study.

The development of cataracts has also been described in another paper.[2] As discussed there, the development of cataracts as viewed by slit-lamp corresponded in all respects to the development of cataracts in human individuals. Histologically also the cataracts corresponded to the picture of human diabetic cataracts. Cataracts seem to develop much more quickly and progress further in rabbits with poorly controlled diabetes than in those receiving insulin.

None of the rabbits so far studied presented evidence of arteriosclerosis. The rabbit is so prone to spontaneous arteriosclerosis that it would seem an unsuitable animal for the evaluation of the relation of diabetes to arteriosclerosis. This would be true even though the percentage of such lesions was to prove high in rabbits which had been maintained in diabetes over a considerable period of time. No physiologic changes suggestive of diabetic neuritis have yet appeared and no degeneration of peripheral nerves was noted in histologic sections.

Comment. This study, as well as numerous investigations in the literature, indicates that the most striking characteristic of the lesion induced by the injection of alloxan is the specificity which it shows for the islets of Langerhans. Furthermore, the beta cells are affected

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most severely and a certain percentage of the alpha cells remains intact. This specificity not only provides an excellent technique for the production of diabetic animals in the laboratory but also presents a problem in the correlation of chemical and morphologic relationships. The changes outside the pancreas are minor in character from the morphologic point of view. This is a further indication of the specificity of alloxan for the islets of Langerhans, and also provides evidence that the animals may be maintained for long periods of time by the administration of insulin without complicating extrapancreatic lesions. From the point of view of the investigator, however, it is unfortunate that the alpha cells are not completely destroyed. Experimental pituitary diabetes can result in destruction of beta cells without destruction of alpha cells. It would be useful if, in alloxan diabetes, there was complete destruction of the islet cells, so that a preparation would be available with the external secreting parenchyma intact but all cells of the islets destroyed. Alloxan, however, does not satisfy these requirements.

There are conspicuous species differences in the extent of extrapancreatic lesions induced by the injection of alloxan. For instance, the lesion of the kidney in the rat[2, and others] is much more severe than are those in the rabbit. The studies reported in this paper indicate that the lesion of the islets of Langerhans after the injection of alloxan begins its development a very short time after the injection has been given and continues in a steady progression to the fully established lesion. There is no break in the sequence at any point. The lesion is degenerative from the beginning and progresses through a stage of almost complete destruction to one of repair by cells which are unable to secrete insulin. For this reason, the explanation for the hypoglycemic phase must be sought elsewhere than in a stimulation of the islets of Langerhans. It seems to us likely that the initial hyperglycemic phase has an extrapancreatic origin and the experiments of Goldner and Gomori[10] indicate clearly that the adrenal is connected with this phase.

The lack of cellular response to the necrosis in the islets of Langerhans is remarkable. In almost all other forms of necrosis, neutrophils may be seen at one stage or another. The response of the islets of Langerhans to alloxan, therefore, offers a biologic problem of considerable interest from the standpoint of general pathology.

The lesions induced by small doses of alloxan are very striking. The number and variety of changes in the islet cells are not reminiscent of any well-known lesion of these islets. For comparable lesions, one is inclined to look for comparison more toward the early sequences in other organs following administration of certain carcinogenic hydrocarbons than to the lesions produced by massive doses of alloxan or to those recognized in human diabetes.

From these considerations, it appears that the injection of alloxan not only provides a useful technique for obtaining diabetic animals in the laboratory and for the study of diabetic complications, but also

provides a useful technique for the study of numerous problems in general pathology.*

Summary. A study of the lesion induced by alloxan at numerous intervals in the islets of Langerhans of the rabbit, indicates that it begins almost immediately after the injection of the material and that it is degenerative from the beginning. Degenerative changes in the islet cells are already apparent in the initial hyperglycemic stages, and in the hypoglycemic stage they progress to a point where they approach those of the diabetic phase. The histologic lesions in the different phases of the blood sugar curve are one continuous process. The pancreatic acini remain normal throughout and changes in organs other than the pancreas are minimal.

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ACUTE YELLOW ATROPHY OF THE LIVER IN EARLY SYPHILIS

A Case Report With Summary of the Literature

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Acute yellow atrophy of the liver occurring in early syphilis is very rare. Its incidence as a complication of acute, *untreated* syphilis is

* Since this paper was submitted for publication, there has appeared a study relevant to this discussion. (Ridout, J. H., Ham, A. W., and Wrenshall, G. A.: Science, **100**, 57, 1944.) This investigation showed by means of insulin assays and histologic studies on the pancreases of rats and dogs after administration of alloxan that "the insulin content of the pancreas did not fall appreciably until after most islet cells were found by histological examination, to be dead. . . . . It appears most unlikely that it exerts its hypoglycemic effect by stimulating islet cell secretion because most of the islet cells are dead when the hypoglycemic phase occurs."

There is thus evidence from physiologic and morphologic studies that alloxan causes hypoglycemia by release of preformed insulin. The hypothesis suggested in our first studies[1] thus receives strong support from two entirely independent investigative techniques.

small, although it is seen more frequently following arsenical therapy. Therefore it seemed worthwhile to report this case, in which jaundice occurred accompanying secondary syphilis, progressing in a few weeks to acute yellow atrophy.

Jaundice occurring in syphilis was noted as early as 1585 by Paracelsus.[29] It was early appreciated that hepatic involvement in acute syphilis might take one of two forms—relatively benign syphilitic hepatitis or grave icterus, a fulminating acute yellow atrophy. Herxheimer[13] estimated that the incidence of jaundice was 0.3 to 3% of all patients with early syphilis. In 1853 Gubler[12] proposed as proof for the syphilitic etiology of this jaundice the five points: (1) that it exists in the absence of other common causes of jaundice; (2) that it coincides with other specific symptoms; (3) that it appears regularly in a determined period of the general infection; (4) that it has a typical course and duration; and (5) that specific treatment leads to a favorable outcome.

The actual pathogenesis of the jaundice in acute syphilis has been difficult to establish because of the paucity of pathologic material. Warthin[45] alone has reported the demonstration of *Tr. pallidum* in the liver of a patient in the secondary stage of adult syphilis. Other theories of the mechanism of this jaundice include interstitial inflammation,[40] hemolytic jaundice,[2,11] roseola of the bile ducts, portal lymphadenitis obstructing the bile ducts, duodenal catarrh, and syphilitic hepatitis.

The introduction of arsenical therapy has further complicated the question of syphilitic jaundice. The hepatotoxic action of the organic arsenicals has been well demonstrated both in experimental animals and in man, with results ranging from mild degenerative changes to acute yellow atrophy. Wile and Sams[49] computed an increase of jaundice in early syphilis from 0.18% in untreated patients to 1.37% in those given arsenical therapy. Although some of these instances of jaundice during treatment are clearly manifestations of arsenic toxicity, substantiated by the evidence of Moore[24] and Sager,[34] others may be syphilitic hepatitis occurring because of insufficient treatment and responding to further antisyphilitic therapy, and still others intercurrent acute catarrhal jaundice. Statistics from large army and navy groups (Soffer,[39] Ruge,[32,33] have shown a striking parallel between the incidence of postarsphenamine jaundice in syphilitic and that of acute catarrhal jaundice (non-specific acute hepatitis) in non-syphilitic men of the same locations.

The mechanisms for the occurrence of jaundice in early syphilis have been variously postulated as:

Untreated (due to syphilis):
- Roseola of bile ducts
- Lymphadenitis compressing bile ducts
- Spirochetosis
- Hyperemia of intrahepatic bile ducts
- Duodenal catarrh
- Hemolytic jaundice
- Syphilitic hepatitis

Treated:
Herxheimer effect
Syphilitic hepatitis with inadequate treatment, hepato-recurrence
Arsenical hepatitis
Bismuth hepatitis
Mercurial hepatitis

Coincidental:
Catarrhal jaundice
Cholelithiasis

The simultaneous occurrence of acute yellow atrophy and syphilis was first recorded in 1836 by Bright.[4] By 1908 Fischer[10] collected a total of about 50 cases from the literature. Osler[28] attributed 10% of all cases of acute yellow atrophy to early syphilis. Since 1914, undoubtedly because of the widespread use of specific treatment, there have been very few cases reported of acute yellow atrophy in untreated syphilis. Survey of the literature to date reveals 59 cases of acute yellow atrophy of the liver in acute syphilis, proven at autopsy, not related to arsenical treatment. Of these, 21 were women, of which at least 2 were pregnant, 15 were men, and the rest not designated. All were between the ages of 2 and 39, most between 16 and 25. Most were in the secondary stage, but 4 occurred during the primary stage of syphilis. In 12 treatment with mercury preparations preceded the onset of jaundice. There have been 2 cases diagnosed as acute yellow atrophy clinically because of decreasing liver size, mental confusion, and the presence of crystals of tyrosine and leucine in the urine, both recovering with specific therapy; Umber's case[44] treated with arsphenamine, and Wile's[48] treated with mercury and iodides.

Since the introduction of the arsenicals, there has been considerable increase in the number of cases of acute yellow atrophy associated with early syphilis. By 1930 Bortin[3] could collect 90 reported cases of acute yellow atrophy following arsphenamine therapy. McDonagh[19] reported 5 cases of jaundice and 1 of acute yellow atrophy in early syphilis seen in the period from 1906 to 1914; from 1914 to 1918 he saw 21 cases of jaundice and 8 cases of acute yellow atrophy in patients whose acute syphilis was being treated by arsphenamine. Neoarsphenamine has been found to be less toxic than arsphenamine (Schamberg[35]). The only report of acute yellow atrophy following treatment with mapharsen was that of Zellermayer.[50]

The similarity of syphilitic acute yellow atrophy to that which follows acute catarrhal jaundice has been pointed out by Senator,[37] Buschke,[5] and Herxheimer.[13]

Clinical Picture. Clinically, acute syphilitic hepatitis differs little from acute catarrhal jaundice. Often there is less systemic reaction—less malaise, fever, or gastro-intestinal symptoms—but this is not sufficiently distinctive to be of diagnostic importance. Only the demonstration of the spirochete or the presence of positive serologic tests for syphilis gives presumptive evidence that syphilis is the cause of the jaundice.

Similarly acute yellow atrophy associated with acute syphilis is no different clinically from that of other causes. It usually begins in-

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sidiously like a benign hepatitis, often with hepatomegaly. There may or may not be fever, malaise, muscle pains, nausea, vomiting, or pruritis. Then rather suddenly there comes a turn for the worse, marked especially by psychic and neurologic disturbances—headache, restlessness, disorientation, delirium, hyperactive reflexes, convulsions—finally coma and death. During this latter phase the liver becomes rapidly smaller. Crystals of tyrosine and leucine often appear in the urine, and frequently the patient has a striking pungent odor, suggestive of acetamide. Terminally there is usually a little fever.

Case Report. M. H., a 15 year old, single, white school girl, was admitted to the Medical Service of the Vanderbilt University Hospital on October 30, 1942, with the complaints of rash and jaundice. Her illness had begun about 3 weeks before with a small round, red, raised, burning lesion on the left labium, occurring about 3 to 4 weeks following last sexual exposure. The genital lesion subsided spontaneously in 3 or 4 days, but about 2 weeks before admission small, round, red, raised, non-pruritic lesions appeared on the labia, and soon after on the face, hands, arms, legs, and feet. About 10 days before admission the urine became dark. Eight days before admission her skin and eyes became yellow, the jaundice deepening progressively to the time of admission. During the week before admission she had malaise, slight fever, anorexia, and nausea. She had received no treatment.

Physical Examination. On admission her temperature was 101° F., pulse 82, blood pressure 116/80. There was marked icterus of the skin, scleræ, and mucous membranes, but the patient did not appear very ill. There was a widespread papular eruption over the entire skin surface, most profuse on the palms and soles. There was a general glandular enlargement, most marked in the inguinal regions. The tonsils were enlarged and inflamed, with mucous patches. Liver and spleen were not palpable, the liver edge being percussed 3 cm. above the costal margin, with the upper border at the normal level. There was considerable inflammation and edema of the vulva with small ulcers, and a profuse white purulent vaginal discharge. Reflexes were hypoactive. During her entire stay a peculiar pungent, mousy odor was noticed constantly in her room.

Laboratory Data. Dark-field examination of scrapings from one of the skin lesions revealed *Tr. pallida.* Wassermann and Kahn tests were strongly positive. The urine contained bile. Stool was light in color, but gave a positive test for bile. Icterus index was 45, van den Bergh test positive immediate direct, prothrombin time 29 seconds (less than 20% of normal). A flat Roentogen ray film of the abdomen showed that the liver was apparently normal in size.

Course. On November 2, after the icterus index had risen to 60, the patient was given 0.015 gm. of mapharsen intravenously and 0.13 gm. of bismuth subsalicylate intramuscularly. That evening the temperature rose to 103° F., and all the skin lesions were surrounded by erythema. On the following day the temperature dropped to normal, and the exacerbation of the skin lesions had subsided. Icterus index was still 60, and serum bilirubin was 23.6 mg. per 100 cc. On November 4, without any specific therapy or any complaints, the temperature again rose to 103.6° F. On November 5, mapharsen 0.03 gm., was given intravenously. The temperature rose to 101° F., but there was no change in the skin lesions. On that day the icterus index was 45. On November 6, she received 0.13 gm. of bismuth subsalicylate intramuscularly, with a subsequent rise of temperature to 100.6° F. On November 8, mapharsen 0.04 gm. was given intravenously. By this time she was afebrile, the skin lesions were subsiding, and the ulcers of the vulva were smaller. However, the jaundice persisted unchanged, with the icteric index 60, serum bilirubin 31 mg. per 100 cc., and prothrombin time consistently less than 20% of normal, in spite of daily injections of vitamin K. On the afternoon of November 10,

the patient said that she felt queer and thought she was going to die, but no objective changes were noted. The next day she complained of extreme weakness, and became progressively more confused and disoriented, with nausea and anorexia. By evening she was stuporous. Her neck was not stiff. Her pupils were widely dilated, but reacted to light. Eye-grounds were negative. The liver edge was questionably palpable in the midepigastrium, but liver dullness was still very small. Reflexes were equal and active. Lumbar puncture revealed clear yellow fluid under pressure of 145 mm. of water, containing no cells. Spinal fluid protein and sugar were normal, and Wassermann test was negative. No tyrosine or leucine crystals were demonstrated in the urine. Icterus index was 60 and remained so until death. On November 12 she was extremely lethargic, and on November 13 it was noted that the left arm was flaccid with very hypoactive reflexes, although all the other tendon jerks were hyperactive. Kernig's sign was negative. There was a positive Babinski reflex bilaterally. On November 15, a sustained clonus was noted in both ankles, and temperature went up to 101.4° F. The following day respirations became labored and stertorous, and many coarse râles were heard throughout the chest. Her temperature was 102.8° F., and leukocyte count 20,000. Sulfathiazole was given by gavage. Lumbar puncture revealed clear yellow fluid under markedly increased pressure, containing 176 red blood cells and 13 white blood cells per c.mm. During this last week she was treated with parenteral glucose and saline, transfusions of fresh whole blood, and oxygen. On the morning of November 17 she developed some muscular twitchings of her face and deep gasping respirations, and died in about half an hour.

Pathologic Report (limited to positive findings): The patient was seen to be deeply jaundiced with the remnants of a generalized red-brown maculopapular eruption involving the scalp, face, extremities, and vulva. The *peritoneal cavity* contained 50 cc. of dark yellow-green fluid. The fat was dark yellow in color, and contained numerous petechial hemorrhages. The peritoneal surfaces were stained yellow and were smooth, shiny, transparent, and glistening. The mesenteric and retroperitoneal *lymph nodes* were enlarged and soft. The posterior portions of both *lungs* were firm and resistant. The epithelial linings of the *bronchi* were hemorrhagic, and there was a small amount of brown frothy fluid in the bronchial lumina. The hilar and mediastinal nodes were enlarged, yellow, and soft. Posterior to the second portion of the duodenum was a small retroperitoneal hemorrhage. The *gastric* rugæ were unduly prominent and hemorrhagic, with moderate edema, but no areas of ulceration. The *liver* weighed 1000 gm., had thin, well-demarcated edges and a smooth, shiny capsule without evidence of wrinkling. It was a bright red color with several small, elevated, yellow nodules on the anterior and posterior surfaces of the right lobe. The liver was of a firmer consistency than normal except for the yellow nodules, which felt like normal liver tissue. The red areas were firm, contained excess fibrous tissue, and did not show the normal liver lobules. The yellow areas contained distorted lobulations. The *gall bladder* was small and contracted, slightly thickened, but with normal, patent ducts, no stones. The *spleen* weighed 280 gm. and showed prominent Malpighian corpuscles and a generally hyperplastic appearance. The *kidneys* were enlarged and soft, with normal shape and contour. The *brain* was slightly softer than usual and generally edematous, but there were no areas of hemorrhage or softening.

Microscopically the *liver* parenchyma appeared disintegrated and necrotic. The remaining liver cells were irregular, distorted, granular, and arranged in cords. Many showed extremely dark nuclei and many clear zones. The remainder of the liver substance was represented by cellular débris, massively infiltrated by small round cells, polymorphonuclear leukocytes, large mononuclear leukocytes, and macrophages. These necrotic areas contained albuminous granules, fat globules, masses of bile pigment. The sinusoids were widely distended, and small foci of hemorrhage were evident. This destruction was generalized, but appeared to be most marked about the central veins. The

vessels were engorged, and their walls showed a small round cell and macrophage infiltration. There was a rather marked bile duct proliferation, about which there was an infiltration by lymphocytes and plasma cells. Scattered throughout all sections there were patchy areas in which there appeared to be a fibroblastic proliferation. The large bile ducts were lined with extremely tall columnar epithelium. The capillary tufts of the *kidneys* were engorged with blood, and many showed hemorrhage on the basement membrane. A few appeared abnormally cellular, due to the presence of macrophages within the tuft. The tubules showed marked cloudy swelling. The *meninges* were thickened and moderately infiltrated by lymphocytes, large mononuclears, and macrophages. The subpial space contained an amorphous pink precipitate. The cellular infiltration accompanied the meninges into the brain substance. The meningeal vessels were markedly engorged with extravasation in many regions. The cortical neurons showed a normal distribution with no significant changes. The perivascular spaces were wider than normal, with occasional small hemorrhages.

The ANATOMIC DIAGNOSES were acute yellow atrophy of the liver, secondary syphilis, acute bronchopneumonia, focal glomerulonephritis, acute uterine cervicitis, cerebral edema and congestion, acute splenic tumor.

Discussion. This patient, then, was a 15 year old girl, who developed jaundice shortly after a secondary syphilitic eruption, and who progressed to acute yellow atrophy of the liver, dying about a month after the onset of jaundice. At the time of admission her liver was small to percussion and apparently about normal size by Roentgen ray—not enlarged as one might expect in a simple syphilitic hepatitis. Acute yellow atrophy was considered at that time, but its extreme rarity and the apparent normal liver contour by Roentgen ray favored the diagnosis of syphilitic hepatitis. Consequently specific therapy was decided upon. The patient developed a typical Herxheimer phenomenon (fever and exacerbation of skin lesions) after the first injection of mapharsen and bismuth, and a much milder one after the second mapharsen injection. The skin lesions began clearing satisfactorily. However, the failure of the jaundice to improve cast some doubt on its syphilitic etiology and suggested an intercurrent acute catarrhal jaundice. About this time the patient became suddenly worse, with stupor, hyperactive reflexes, clonus, positive Babinski reflex, dilated pupils. The predominance of neurologic symptoms with negligible fever or gastro-intestinal symptoms and the onset 3 days after the last injection suggested hemorrhagic encephalitis caused by mapharsen, or a cerebral hemorrhage related to the prothrombin deficiency. However, the autopsy showed typical acute yellow atrophy of the liver, with only cerebral edema, no hemorrhagic lesions in the brain.

The question arises as to the nature of this patient's liver disease. Did she have syphilitic hepatitis resulting in acute yellow atrophy because of the added hepatotoxic effect of mapharsen? Did she have acute yellow atrophy from the onset? Did she have acute catarrhal jaundice? Would she have recovered on heavy metal therapy, or on more vigorous arsenical therapy? These questions cannot be answered with our present knowledge. We doubt that her death was due solely to arsenic, since of her three doses only the last was of therapeutic size. The occurrence of the jaundice almost simultaneously with the secondary syphilitic eruption strongly suggests that it was syphilitic in

origin. If the jaundice was due to syphilitic hepatitis, we believe that it was probably a grave form from the onset and progressed to acute yellow atrophy in spite of treatment. The other possibility, an acute infectious hepatitis, cannot be ruled out.

From an extensive search of the literature there have been collected 31 cases of syphilitic hepatitis with jaundice, in which arsenical therapy brought about rapid clearing of the jaundice. *Not a single instance has been found in which the use of arsenic in the presence of jaundice resulted in acute yellow atrophy.* Thus, our case is unique. This patient had secondary syphilis and jaundice, was given mapharsen and bismuth, and subsequently died of acute yellow atrophy of the liver.

TABLE 1.—SYPHILITIC HEPATITIS TREATED BY ARSENICAL PREPARATIONS

Author	Sex	Age	Stage	Treatment before jaundice	Diagnostic proof	Treatment after jaundice
Duhot[8]	M	49	1	Hebetin	DF	Arsphenamine
Umber[41]	F	19	2	"Mixed treatment"	W	Arsphenamine
Milian[22]	F	..	2	Neoarsphenamine	..	Neoarsphenamine
Scott & Pearson[34]	M	21	2	.....	..	Neoarsphenamine and mercury
	M	21	..	.....	..	Neoarsphenamine and mercury
Milian[23]	F	21	2	.....	DF	Neoarsphenamine and mercury
	M	38	2†	Olarsol and neoarsphenamine	..	Neoarsphenamine and mercury
Chatellier[6]	F	22	1, 2	.....	DF, W	Neoarsphenamine
Benesch & Crehange[1]	F	24	1, 2	.....	..	Arsenical
Nicaud[25]	F	32	1, 2	.....	DF	Neoarsphenamine
Nicaud[26]	F	23	1, 2	.....	W	Arsphenamine and mercury
Tobias[42]	F	20	2	.....	DF, W	Arsphenamine
Mattes[24]	6 or 7 cases			.....	..	Arsphenamine
Tzanck[43]	..	..	..	Arsenical (3 doses)	..	Arsenical
			2	Neoarsphenamine	W	Arsenical
Waugh[46]	F	25	2	.....	Kl, Ka	Neoarsphenamine
	M	22	1, 2	.....	Kl, Ka	Neoarsphenamine and bismuth
Creswell[7]	M	19	2	.....	W, Ka	Bismuth and arsenoxide
	M	26	1	.....	W, E	
Lane[17]	M	29	2	.....	..	Arsphenamine and bismuth
Moore[21]	3 or 4 cases			.....	..	Arsenical
Rattner[30]	M	33	2	.....	DF, W	Neoarsphenamine
Kampmeier[15]	M	..	2†	.....	W	Neoarsphenamine
Kampmeier[16]	M	30	2†	.....	DF, W, Ka	Neoarsphenamine

† Relapse.
1, primary; 2, secondary; DF, dark-field; W, Wassermann; Ka, Kahn; Kl, Kline; E, Eagle.

The accompanying table summarizes the reported cases of patients with syphilitic hepatitis, who were treated with one of the arsphenamines. It was interesting to compare these results with those obtained by treatment with mercury, iodides, and bismuth. Heavy metals alone brought about clearing of the jaundice in most cases, but after an average of 1 or 2 months instead of 1 to 3 weeks. One may question whether some of the patients who died of syphilitic acute yellow atrophy in spite of treatment with mercury or bismuth might have been saved by arsenical therapy. Since improvement with heavy metal treatment was very slow, it is reasonable to doubt whether it had any appreciable effect on the syphilitic hepatitis, or whether the jaundice in those cases cleared spontaneously.

This brings up the still debated question of the best way to treat patients with jaundice in acute syphilis. Because of the occurrence

of jaundice after arsenical treatment and the experimental evidence of the toxicity of arsenic for the liver, there has been prejudice against the use of arsenical therapy especially at the onset of treatment. Scott and Pearson[36] advocated preliminary treatment with mercury and iodides for several weeks to months, then cautious use of an arsphenamine. Wile,[47] although admitting the brilliant results sometimes achieved with arsenical therapy, recommended that it not be used as a routine measure in hepatic syphilis. Elliott and Todd,[9] Smith,[38] and MacDonald[20] believed that arsphenamines were contraindicated. O'Leary[27] advised the prolonged use of preparations of mercury and iodides preliminary to the use of arsphenamine. Stokes,[41] in benign hepatitis, recommended bismuth until the icterus index returned to normal, then arsphenamine in moderate doses. For grave icterus he felt the vigorous use of bismuth the best treatment.

On the other hand, Umber[44] reported a case of jaundice in acute syphilis, diagnosed acute yellow atrophy because of the rapid decrease in size of the liver and the presence of leucine and tyrosine crystals in the urine, which responded well to arsphenamine, making a rapid recovery. He advised that in acute yellow atrophy with a positive Wassermann test one should not delay arsphenamine therapy. Langevin and Brule[18] considered the hepatotoxic action of arsphenamine negligible compared with its therapeutic activity. Mattes,[21] in discussing Smith's paper, cited 6 or 7 cases treated with arsphenamine, recovering without complications. Rolleston[31] recommended that the treatment be that of the syphilis, not that of jaundice. Irgang and Sala[14] believed that the presence of a mild syphilitic hepatitis was no contraindication to arsphenamine therapy. Waugh[46] reported good results from the use of arsphenamine. In early syphilitic hepatitis, Moore[24] advised the use of arsphenamine as in uncomplicated early syphilis, starting with smaller doses, but working up quickly to the usual therapeutic dose. In all his (3 or 4) observed cases the jaundice rapidly cleared, there were no evidences of decreased tolerance for the arsenicals, and the patient's subsequent progress was uneventful. As to acute yellow atrophy in early syphilis, he reported that it "is so rare that we have never seen a case. Reported instances have been so rapidly progressive and the prognosis so grave that therapeutic efforts can not be limited to the slower acting heavy metals. Neoarsphenamine or mapharsen should be employed."

No one person sees enough of such patients to be able to accumulate an adequately controlled series. In view of the incompleteness of clinical evidence of deleterious effect of arsenical therapy in the jaundice of early syphilis, and the reports of prompt relief of symptoms by specific therapy, we believe that the published weight of evidence is in favor of its use. We must bear in mind, however, the general tendency not to report unfavorable cases. Many patients have been cured of their jaundice by mercury, iodides, or bismuth, or even without treatment. However, some of these patients die of acute yellow atrophy, whereas the case here reported is the only one known in which arsenical treatment of early syphilitic jaundice has been followed by

acute necrosis of the liver. And it remains to be shown which causes the more permanent liver damage and loss of liver function, the rapidly acting, more toxic arsphenamine, or a more prolonged course of syphilitic hepatitis.

Confronted with this identical situation again, we still would not be sure of the correct answer as to therapy. In spite of the fatal outcome of this patient, we believe that the evidence gathered from the literature justifies the use of arsenical treatment in acute syphilitic hepatitis. We are of the opinion that vigorous treatment with one of the arsenical preparations and bismuth, together with the usual supportive measures in liver disease—high carbohydrate, high protein, low fat diet, adequate fluids, high vitamin intake, transfusions—offer the best chance for success.

Conclusions. 1. An unusual case of acute yellow atrophy in secondary syphilis with death after 3 injections of mapharsen and 2 of bismuth is reported.

2. The literature concerning jaundice in acute syphilis, its pathogenesis and treatment, has been briefly summarized.

3. Syphilitic hepatitis responded favorably to arsenical treatment in all the 31 reported cases.

4. Although knowledge of the subject is incomplete, and although our patient died of acute yellow atrophy after a small amount of mapharsen therapy, we believe that until the cases with bad effects have been adequately reported, we can only say at present that the literature supports the stand that the use of the arsphenamines in the treatment of jaundice in acute syphilis is justified.

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OBSTRUCTION OF THE HEPATIC VEINS (CHIARI'S DISEASE)

Report of Five Cases

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In this paper we are reporting 5 cases of a rare disease, hepatic vein thrombosis. This condition was described by Budd[4] as early as 1846, and endophlebitis of these veins was recognized as a pathologic entity by Chiari[7] in 1899. The clinical aspects were defined by Hess[12] in 1905 and by Thompson and Turnbull[25] in 1912. Two instances of neoplasm obstructing the hepatic veins were reported in the next decade,[15,27] and Hoover[13] in 1920 found 30 cases in the literature. A tabular synopsis of cases reported since 1920 is given in Table 1.

A variety of etiologic factors has been reported for hepatic vein obstruction. They include primary thrombosis and thrombophlebitis;[4,12] primary endophlebitis;[7] local and general infection;[6,23] stasis;[2] systemic disease, in most cases polycythemia vera;[1,2,3,8,19,21,24,26] and mechanical obstruction by anomaly[7,12] or neoplasm.[14,15,27] Early writers favored alcoholism,[4] syphilis[7] and mechanical stresses asso-

ciated with pregnancy[25] or chronic cough[12] as causative agents, but these must be exceedingly rare. Only one definitely positive Wassermann reaction appeared in one series of 8 cases.[5]

Thrombosis occurs most frequently where the hepatic veins empty into the inferior vena cava, perhaps because of eddy currents formed at the oblique entering angle.[2,13,15] As thrombosis of the hepatic veins is often accompanied by inflammatory changes in the inferior vena cava,[3,22] it is probable that the two processes are often continuous, proximity and eddy currents aiding in the spread of infection from one vein to the other. Hepatic vein thrombosis may be partial or complete,[13] or complete with recanalization.[2,14,19] Collateral circulation is common when the obstruction occurs gradually,[25] and the ratio of collateral circulation to circulation lost by obstruction determines the symptoms experienced by the patient.[14] Postmortem examinations show a characteristic central necrosis of the liver lobules, congestion of blood in this locality, replacement fibrosis of the liver, and enlargement of the spleen.[14] Enlargement of the liver is due to engorgement, the organ being actually smaller than normal when the blood has been removed.[1]

Hepatic vein obstruction appears with equal frequency in men and women ranging in age from 17 months (cited[12]) to 70 years.[16] Most cases (over 50% in Table 1) occur between the ages of 20 and 40 years.[9,12,16] The disease may appear in the acute or the chronic form.[12] The acute form[1,2,3,6,9,21] is sudden in onset with obscure abdominal pain, nausea, vomiting, abdominal guarding and shock,[9] followed by ascites, tenderness and enlargement of the liver and spleen, delirium, coma and death in 1 to 4 weeks. The chronic form is gradual in onset, with indigestion, epigastric pain, ascites and tender enlargement of the liver, collateral circulation, cyanosis, rarely jaundice; with eventual coma, delirium and death—often within 6 months, sometimes after several years.[10,14,22,23,24] Cases with prolonged survival reported without autopsy[13] are open to question, although life is possible in the presence of limited thrombosis of the hepatic vein with incomplete occlusion of the vein, early recanalization, or the development of adequate collateral circulation. Symptoms may not appear until hepatic vein occlusion is almost complete.[13]

Pain over the liver, sometimes radiating to the back and shoulders, rapid accumulation of ascites resistant to diuretics, simultaneous enlargement of a smooth-edged liver and spleen, development of a collateral circulation and edema of the legs suggest hepatic vein obstruction. There may be signs of associated disease, notably infection or polycythemia vera, of which hepatic vein thrombosis may be considered a severe complication.[24] In several cases ascites has been associated with pleural fluid.[1,13,19]

Jaundice and bilirubinuria are infrequent.[13] There may be a lowered plasma cholesterol with absent ester fraction,[1,24] and an elevated blood urea.[1]

The terminal episode is usually coma occasioned by hepatic insufficiency, although there may be oliguria and acidosis[15] and a state

TABLE 1.—TABULAR SYNOPSIS OF CASES OF CHIARI'S DISEASE REPORTED SINCE 1920

Reported by	Age	Sex	Duration	Type of death	Symptoms and signs	Ascitic fluid	RBC (mill.)	Hb.)%)	WBC (thous.)	Other laboratory data	Findings in hepatic veins at autopsy
Hoover[13]	?	M	..	Lived	Abd. pain, liver enl., ascites, pleural eff.	Opalescent, 1.014 (27 abd. taps), occ. WBC	4.8	65	1.2	Nor. bile formation and excretion	
Hoover[13]	31	M	..	Lived	Ascites, liver enl., pl. effusion	Clear yellow, 1.008, 600 cells (? type)	..	..	..	? Wass.	
Oppenheimer[21]	19	F	3 wks.	..	Ascites, liver enl., spleen enl.	....	8.83	124	3.4	360,000 platelets	Platelet thrombus
Baehr and Klemperer[2]	49	F	3 wks.	Postop. collapse	Abd. pain, liver enl., spleen enl., jaundice	Clear yellow, 2000 cc.	6.0	110	9.9	....	Recanalized thrombus
Hutchison and Simpson[14]	28	M	? 25 yrs. or 1 mo.	Postop. collapse	No ascites	....	..	..	..	Wass. neg.	Occlusion, anast. with veins of diaphragm
Cole[8]	33	M	4 mos.	Coma	Liver enl., spleen enl., ascites	23 abd. taps removing 147 liters	8.6	120	17.1	Wass. neg.	Thrombosis
Rigdon[22]	22	F	Recurrent	Hemorrhage	Recurrent ascites for 2½ yrs.	Clear yellow, 1.013, protein 1.19 mg. per 100 cc., cholesterol 65 mg. per 100 cc.	4.56	94	10.1	Wass. neg., BMR −22%	Phlebitis of hepatic and portal veins and inf. vena cava
East[10]	38	M	..	Lived	Liver and spleen enl., ankle edema, collat. circ.						
Cambrier and Dagnelie[6]	51	M	2 wks.	..	Signs of generalized infection	....	4.9	102	11.6	Old lues	Thrombosis
Savin[23]	27	M	2 mos.	..	Liver enl., ascites, collat. circ.	....	..	..	..	Wass. neg.	Antemortem clot
Sohval[24]	30	M	2 mos.	Postop. (omentopexy)	Liver enl., ascites, jaundice, pleural eff.	Bile stained	7.43	110	27.5	Wass. neg., PCV 60%, II—22, 220,000 platelets	Thrombosis
Ulhorn[26]	38	F	..	..	Spleen enl., jaundice	....	8.7	110	49.7	....	Old thrombosis
Berk[3]	56	F	1 mo.	..	Abd. pain, liver enl., spleen enl., ascites, jaundice	....	7.2	115	12.0	Wass. neg.	Old thrombosis
Norman and Allen[20]	54	F	..	..	Spleen enl., ascites	....	..	..	..	....	Recanalized thrombosis
McAlpin and Smith[19]	57	F	..	..	Liver enl., ascites, jaundice	....	6.8	125	8.3	....	Recent and old thrombosis
Altschule and White[1]	27	M	4 wks.	Coma	Spleen enl., ascites, pl. effusion, jaundice	Clear yellow, 800 cc., 1.015, 2.8 mg. per 100 cc. protein	6.7–6.9	121–132	11.0–21.0	....	Thrombosis
M.G.H. Case 27431[17]	62	M	3 wks.	Coma	Abd. pain, jaundice, signs of infection	....	4.0	60	18.4	van den Bergh biphasic	Thrombosis (with cholangitis and abscess)
Kahn and Spring[16]	21	F	1 mo.	Coma	Abd. pain, spleen enl., nausea	....	4.1	78	14.2	Alb., blood sugar 118.4 mg. per 100 cc.	No postmortem
Dickinson[9]	26	M	2½ days	Postop.	Abd. pain, liver enl., spleen enl., ascites, vomiting, diarrhea	Clear straw-colored, 2500 cc.	..	..	16.1	Wass. neg.	Acute complete thrombophlebitis
M.G.H. Case 29192[18]	42	M	..	..	Ascites	....	..	66	6.7	40% BSP retent., 26 sec. prothr. time, 1+ cephalin-cholesterol flocculation	Thrombophlebitis

approximating the so-called hepatorenal syndrome.[16,28] Sudden swelling of the liver and onset of acidosis, when superimposed upon signs of inferior vena cava obstruction, probably indicate occlusion of the hepatic veins.[15]

Hepatic vein obstruction is rarely diagnosed during life, as the clinical picture is that of portal vein obstruction and hepatic insufficiency. Liver enlargement, jaundice and ascites are, however, more marked in hepatic than in portal vein obstruction;[24] collateral circulation tends to flow caudad in hepatic vein obstruction and cephalad in inferior vena cava obstruction;[25] and the smooth, tender liver and more rapid formation of ascites distinguish hepatic vein obstruction from cirrhosis. In its acute form, Chiari's disease may be mistaken for a surgical emergency,[9] and the chronic form has been closely simulated by primary tumor of the inferior vena cava without hepatic vein involvement.[11]

No method of treatment has been suggested; patients have died shortly after attempts at omentopexy[24,25] and after other operations.[9,14,16,21]

Almost 60 instances of this disease have now appeared in the literature, but the cases are still isolated, and more frequent reports may be expected to follow more careful routine postmortem examination of the hepatic veins.[5,12] Only 5 instances of hepatic vein thrombosis have been found among the 11,979 autopsies done by members of the Stanford Department of Pathology since 1898, an incidence of 0.042%. These 5 cases are described below; the most recent, about which more details are available, is set forth at greater length.

Case Reports. CASE 1. J. H., a 28 year old Mexican, entered the hospital on October 27, 1926, after 5 days of fever, cough, pleurisy, abdominal pain and constipation. The pain in the abdomen had begun gradually in the epigastrium and right upper quadrant and the abdomen had rapidly enlarged.

Physical examination showed a blood pressure of 92/66, the pulse was 100 to 140 per minute, and the respirations 28 to 35 per minute. There was a bilateral bronchopneumonia. The abdomen was greatly enlarged and tender in the right upper quadrant and there was marked enlargement of the liver.

The red blood cells numbered 4.8 million with 85% hemoglobin and 15,000 white blood cells (83% neutrophils). The urine contained many hyaline casts. The Wassermann test was negative. The spinal fluid was under normal pressure and gave a negative Pandy reaction.

The patient died 4 days after entry.

Postmortem examination (30–46) revealed 250 cc. of slightly turbid dark yellow fluid in the abdomen. The liver was enlarged and adherent to the diaphragm, beneath which lay an abscess filled with thick creamy pus and 1.5 cm. in diameter. Fibrous tissue connected this abscess with a second abscess which lay within the substance of the liver and measured 4 cm. in diameter. There were recent thrombi in many small and several large hepatic veins. Histologic examination showed the liver to be hyperemic and edematous. Cultures taken from the abscesses grew Hiss-Russell dysentery bacilli, *B. coli*, and non-hemolytic streptococci. No amebæ were found.

CASE 2.—F. R., a 56 year old white male, entered the hospital November 20, 1934, because of an epigastric mass of 1 month's duration. A duodenal ulcer has been diagnosed by Roentgen ray in 1926 and the patient had obtained some relief with diet.

Physical examination showed an emaciated man with an easily palpable irregular epigastric mass. The lymph nodes were not enlarged.

The blood and urine were not remarkable in 1933 but the hemoglobin fell to 51% in December, 1934, and 30% in February, 1935, when the serum proteins were 4.2 gm. per 100 cc. (albumin 2.6 gm., globulin 1.6 gm.). The patient became progressively weaker, developed edema of the extremities and died on March 1, 1935.

Postmortem examination (38–245) showed a scaphoid abdomen which contained 1000 cc. of slightly turbid blood-tinged fluid. An extensive, ulcerated carcinoma encircled the pylorus of the stomach and extended into the pancreas, omentum, adrenals and liver. The left main branch of the hepatic vein contained a laminated antemortem thrombus.

CASE 3. F. G., a 55 year old Chilean male, entered the hospital on April 25, 1936. The patient had for years taken daily a quart of wine; in 1906 he had noted a penile sore. In 1928 he vomited 500 cc. of blood, and in 1932 his abdomen became distended and he required a number of paracenteses. Physical examination in 1932 showed a blood pressure of 112/70. There were telangiectases on the nose; the pupils were slightly irregular. The heart and lungs were not remarkable but the abdomen was distended and presented a fluid wave. Liver dullness extended 5 cm. below the right costal margin, and a firm smooth spleen was palpable 3 cm. below the left costal margin. There were a few dilated veins on the abdomen. Four thousand cc. of yellow fluid were withdrawn.

The white blood cell count ranged from 2100 to 7000 with a 48% lymphocytosis. The urine was negative. A blood Wassermann was positive in 1932 and 1934. The spinal fluid was Wassermann-negative with a Lange curve of 1112211000. The Takata-Ara test was negative.

The patient was given liver, insulin and antiluetic treatment. After May, 1935, his ascites seemed to respond to mercurial diuretics, and he remained in fair health in spite of small hematemeses until April, 1936, when he suddenly vomited 1500 cc. of blood. He was admitted to the hospital *in extremis*, the spleen was palpable 3 cm. below the left costal margin and there was shifting dullness in the flanks. The patient died 2 days later.

Postmortem examination (39–426) showed no free fluid in the peritoneal cavity. The liver was small. The spleen was large and covered with adhesions. Large collateral veins (considered at the time to be congenital malformations) passed from the spleen to the left kidney, abdominal wall, and diaphragm. The esophagus contained large varicose veins, several of which were perforated. The portal vein was filled with organizing thrombus and the right and left hepatic veins were thrombosed, the thrombi containing one or two small vessels. More peripherally, thrombi extended into the splenic, gastric and superior and inferior mesenteric veins and could be followed out to the smallest omental veins. The liver was not remarkable histologically.

CASE 4. H. D., a 34 year old white male, entered the hospital on October 15, 1938, after 1 month of weakness, malaise and throbbing pain in the left upper quadrant. An operation 6 days later disclosed a hypernephroma on the left with extension of tumor into the left renal vein. The kidney was removed and the patient left the hospital in 3 weeks, feeling well except for moderate chest pain and wheezing. Chest and bone Roentgen rays, taken at intervals, were negative until October, 1939, when there were small nodular metastases in both lungs. These did not respond to irradiation. In February, 1940, the liver was enlarged, and 1 month later fluid was present in the chest and abdomen. The superficial abdominal veins were prominent. The patient became icteric, failed rapidly and died on April 20, 1940.

Postmortem examination (OD–177) showed 1000 cc. of slightly bloody, semigelatinous fluid in the abdomen. The liver was large and contained 2 large tumor nodules. The entire inferior vena cava from the level of the renal veins to the right auricle was filled with soft, pale yellow to green, friable tumor. All of the branches of the hepatic vein close to and entering the inferior vena cava contained tumor, and on section even the smallest branches were thrombosed.

Histologic examination of the liver showed that the central vein and the sinuses of the central two-thirds of almost all the lobules were filled with blood and the liver cells in this area were atrophic or dead. The radicals of the hepatic vein were filled with organizing thrombus; fibroblasts were growing in from the periphery.

CASE 5.—Mrs. M. McD., a 40 year old English housewife, entered the hospital on February 15, 1937, after several years of low back pain, abdominal pain and dysuria. The patient had borne 2 living children, had once aborted spontaneously and thrice herself induced abortions. There was no history of alcoholism, and the family and past history were unimportant save for the fact that a positive Wassermann had been discovered in 1930 when her husband had a penile chancre. The patient received about 7 intramuscular injections over a 3 month period, then failed to return for treatment.

TABLE 2.—LABORATORY DATA (MRS. McD.) FROM 1937 TO 1942

Date	RBC (mill.)	Hb. (%) (S)	WBC (thous.)	Differential				Packed cell vol. (%)	MCV MCHC MCHbC
				Neutr. (%)	Lys. (%)	Monos. (%)	Platelets (thous.)		
2-15-37	5.7	86	12.6	68	26	3			
8-14-40	5.6	96	14.7	87	11	2			
8-17-40	..	..	9.7	74	24	1			
7- 5-42	5.3	**110**	18.4	88	7	5			
7- 6-42	5.1	100	16.8	..	..	..	230		
7- 7-42	**6.2**	94*	22.6	81	16	2	309	53	85.5 25.8 30.2
7-11-42	5.2	106	24.2						
7-13-42	5.2	103	32.1	86	6	1			
7-16-42	6.0	102†	**29.3**	85	7	4	**361**	58	96.2 28.7 29.8
7-22-42	5.4	101	29.0	82	14	3			

* 16 gm.

† 17.3 gm.

Explanatory notes: MCV—Mean Corpuscular Volume in cu. micra (normal 80-94). MCHC—Mean Corpuscular Hemoglobin Concentration in micromicrograms (normal 27-32). MCHbC—Mean Corpuscular Hemoglobin Content in per cent (normal 33-38).

Physical examination revealed only relaxation of the pelvic floor, old lacerations of the cervix, and chronic cervicitis. The blood pressure was 120/90; no organs or masses were palpable in the abdomen. The blood and urine were normal; the blood Wassermann was strongly positive. Cervical smears showed no gonococci.

A trachelorrhaphy and perineorrhaphy were done; the patient recovered and she was discharged, failing to return to the syphilis clinic as directed.

The abdomen was not found to be remarkable in August, 1940, when the patient entered the hospital for treatment of pelvic inflammatory disease. On this entry, the blood Wassermann was negative, although the patient remembered only 1 or 2 intravenous injections since 1937. On August 21, 1940, a lumbar puncture yielded a clear colorless fluid without cells. The total protein was 33.4 mg. per 100 cc., and there was a strongly positive Wassermann reaction with 0.1 cc. of spinal fluid. The colloidal gold curve was 5555421100.

On May 12, 1941, there was no clinical evidence of syphilis; but now the blood pressure was 160/90. The liver descended 1 cm., and the spleen 3 cm. below the costal margin. During the following period from May 25, 1941,

until June 19, 1943, the patient received irregular treatments consisting of 26 injections of a bismuth compound, 12 injections of Mapharsen, and 3 of silver arsphenamine. Following these injections she occasionally had chills and fever and jaundice without other signs of toxicity.

The patient entered the hospital for the last time on July 5, 1943. In the preceding 2 months she had had 3 spells of indigestion lasting about a week. She had not vomited or been icteric but had passed a tarry stool 1 week before entry. Five days before entry she noticed a swelling of her abdomen and 2 days later the onset of constant upper abdominal pain, perhaps associated with a darker color of the urine. There had been no change in weight.

Physical examination showed a flushed, sick-looking, slightly icteric woman. There were no spider angiomata. The heart and lungs were not remarkable; the blood pressure was 150/110. The abdomen was tense and protuberant with a definite fluid wave. The liver was tender, smooth and firm and descended 1 cm. below the costal margin; the spleen 4 cm. The surface veins of the lower abdomen were full, but no collateral circulation had been established.

The blood counts upon this and the previous entries are entered in Table 2. The urine, stool and Wassermann examinations were not abnormal. A van den Bergh test was positive in the direct phase with an indirect value of 2.2 units. The icterus index was 17. The sedimentation rate was 18 mm. in 1 hour (Wintrobe), and the packed cell volume was 53%. The serum protein (Kagan) was 6.1 gm. per 100 cc.; the bleeding and coagulation time and the prothrombin time were normal. A bromsulphalein test showed 100% retention in 5 minutes and 80% retention in 45 minutes. After injection of Congo red, 60% of the dye was recovered from the plasma in 30 minutes, 71% in 1 hour.

A chest film showed elevated diaphragm on both sides and an old interlobar pleurisy on the right; the heart shadow was not remarkable. A barium meal revealed a normal esophagus, stomach and duodenal cap.

The gastric contents were normal in volume and acidity. The spinal fluid contained 6 lymphocytes, 23.8 mg. of protein per 100 cc. showed a 5555321000 colloidal gold curve and a positive Wassermann reaction with 0.5 cc. of spinal fluid. Electrocardiograms demonstrated a left axis deviation, a small T_2 and an inverted T_3.

On the 5th and 14th hospital days 2200 cc. and 4400 cc. of yellow-orange ascitic fluid were removed. The specific gravity of this fluid was 1.010, cultures were negative, and the sediment contained a few lymphoid and polymorphonuclear cells in equal proportions.

Careful study of a blood film showed 0.4% reticulocytes, some variation in the size and shape of the red blood cells, and an occasional normoblast and myelocyte with a shift toward nuclear immaturity. Sternal marrow puncture material showed (Dr. H. A. Wyckoff): "Normoblasts and megaloblasts of the pronormoblastic type . . . . relatively increased in numbers. . . . . myeloblastic cells—somewhat more than usually numerous. These relationships together with rather more than usually numerous mitotic figures suggest hyperplasia of the marrow with especially active multiplication of erythroblastic cells of the normal series type."

On the 20th hospital day the patient complained of weakness; 2 days later she became much weaker and more listless, a blood sugar was 108.7 mg. per 100 cc. Four hours later her respiration became slow and difficult, her pulse slow and full. She was covered with perspiration, became delirious, then comatose, and died in spite of supportive measures.

Postmortem examination (2D–216) showed a distended abdomen containing 2200 cc. of clear yellow fluid. The liver extended 3 cm. below the costal margin. The peritoneal surfaces were smooth and glistening, but the gall bladder, pelvic organs and spleen were involved by adhesions. These adhesions and the peritoneal surfaces were extremely vascular.

The thoracic cavity contained no appreciable free fluid. There were collections of inflammatory cells in the myocardium suggestive of an acute localized

myocarditis. There was edema of the lungs which contained many recently infarcted areas. No esophageal varices were found.

Histologic examination of the spleen and liver showed numerous scattered small islands of hematopoiesis. Sections of the main hepatic veins near their emergence into the vena cava showed an almost complete obliteration by organizing thrombi with some degree of recanalization at their margins. The vein walls were not abnormal and contained no preëxisting intimal plaques. There was a slight lymphocytic infiltration of the walls and an increased vascularity of the adventitia. Other hepatic veins deeper in the liver were occluded by old partially recanalized thrombi and throughout the liver most of the lobules showed necrosis of the central liver cells and dilatation of the central liver sinusoids. A section of the intrahepatic portion of the inferior vena cava was not remarkable except for a small intimal plaque which appeared to be an advanced stage in the organization of a thrombus. Similar plaques were found in the portal and splenic veins and even in a small vein of the pancreas.

No syphilitic lesions were found, even in the central nervous system.

Discussion. These cases illustrate several clinical and pathologic types of hepatic vein thrombosis. In Case 1, infection was a predisposing factor. In Case 2, the thrombosis was associated with metastatic gastric carcinoma, and in Case 4 with the typical dissemination of hypernephroma along the inferior vena cava. In Cases 1, 2 and 4 thrombosis was unimportant as a cause of death and probably occurred just before the patient expired.

Cases 3 and 5 had hepatic vein thrombi which showed recanalization, and each patient had established some collateral circulation. In Case 3 thrombosis may have occurred 4 years before death, yet the restoration of blood flow was such that the patient survived to die of esophageal hemorrhage.

Case 5 developed thrombi in the portal and hepatic venous systems over an unknown length of time. The enlarged liver and spleen 14 months before the final episode, and the indigestion, ascites and abdominal pain 4 months before death presumably indicate episodes of hepatic vein thrombosis. These thrombi eventually led to hepatic insufficiency. No esophageal varices developed although the passive hyperemia of the liver was extreme.

Long-standing and inadequately treated syphilis seemed to have no etiologic significance in Cases 3 and 5.

Only Case 5 exhibited polycythemia; and, although in this patient the red blood counts were slightly elevated for several years, the bone marrow was hyperplastic and there was extramedullary hematopoiesis in the liver and spleen. Still the evidence for polycythemia vera is much less striking than in the majority of cases with both polycythemia and hepatic vein thrombosis.

Summary. Five cases of obstruction of the hepatic veins (Chiari's disease) are reported with autopsy findings. The literature is reviewed and cases of this condition reported since 1920 are gathered in a tabular synopsis. The diagnosis is rarely made during life. It should be considered in any patient with progressive tender enlargement of the liver and spleen accompanied by ascites and abdominal pain.

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MENINGOCOCCAL INFECTION

I. Meningococcal Meningitis and Septicemia

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Significant changes in the treatment of meningococcal infections have been brought to the attention of most medical officers who have been on duty in station hospitals in the United States during the past year. As the result of a number of epidemics of meningococcal meningitis of sizeable proportions since 1938, several reports[1–5] on the use of sulfonamides as the sole therapeutic agents have appeared in the literature. Their use was further emphasized by War Department Circular No. 17, dated 23 February 1942 issued by the Surgeon General's Office. Data accumulated from a variety of sources—(1) personal communications from members of the Preventive Medicine Division of the Surgeon General's Office, (2) from the Medical Consultant of the Sixth Service Command, (3) from Chiefs of the Medical Services of other Station Hospitals, and (4) from reports in the literature—

indicate that sulfadiazine and its sodium salt is the drug of choice because of its high degree of therapeutic efficiency, its low toxicity, and the infrequency with which complications appear after its use. Our own experience with 61 cases seen and treated at this Station Hospital bears out these observations and serves as the basis for this report.

Epidemiology. Between December 12, 1942 and July 29, 1943, 61 cases of meningococcal infection were admitted to the Station Hospital, Camp McCoy, Wis.; 58 of these patients were soldiers and 3 were civilians. Epidemiologic factors were in accord with those usually

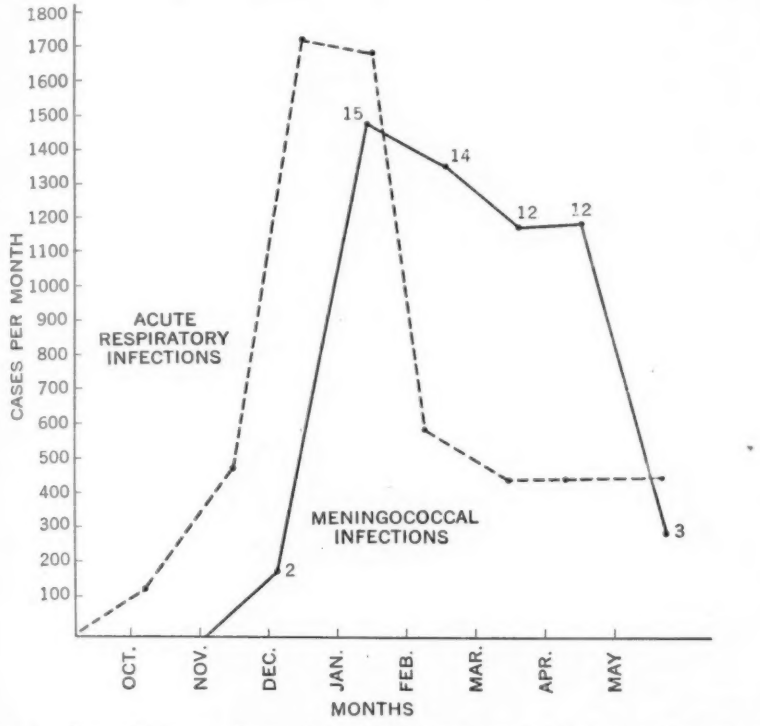

CHART 1.—Cases of acute respiratory infection and meningococcal infection admitted to hospital per month.

recorded: (1) there was no evidence of cross-infection because in no instance did more than one case appear in a single barracks or company; (2) 82% of the soldier-patients were raw recruits; their average age was 23 years and their average time of service was 2.7 months; (3) there had been unusual exposure to severe weather conditions in many instances; (4) there was a degree of overcrowding, impaired ventilation, and increased fatigue. A survey for meningococcus carriers was deemed impractical because of lack of adequate laboratory facilities, nor was it believed that such a survey would serve any useful purpose. Sixty to 70%[4] of the population has been found to

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TABLE 1.—SUMMARY OF 53 CASES OF MENINGOCOCCAL MENINGITIS

Patient	Age	Months of service	Symptoms prior to admission: Duration (days)	Chill‡	Upper respiratory infection	Headache	Myalgia	Arthralgia	Restlessness	Vomiting	Nuchal rigidity	Kernig	Apathy	Coma	Respiratory rate	Admission temp.	Rash
1	20	28	1	+	+	+	+	0	+	+	+	+	0	0	26	104	0
2	22	2	1*	0	+	+	+	0	+	+	+	0	0	0	24	101	0
3	28	2	2	0	+	0	+	+	+	0	+	0	0	0	24	98	+
4	21	2	1	+	+	+	+	0	+	+	+	+	0	0	32	103	0
5	32	2	1	+	+	+	+	0	+	+	+	+	0	0	32	101	0
6	21	4	1	+	0	+	+	0	0	+	+	0	0	+	28	99	+
7	21	2	1−	+	+	+	+	0	0	+	0	0	0	0	24	98	0
8	37	1	1−	0	+	+	+	+	0	0	0	0	0	0	28	99	+
9	23	7	1	0	0	+	+	0	+	+	+	+	0	0	26	98	+
10	33	8	1−	+	+	0	+	+	0	+	0	0	+	0	32	103	+
11†	25	1	1	+	+	0	+	+	0	+	0	0	+	0	24	101	+
12	22	1	1	0	0	+	0	0	+	+	+	+	0	0	30	100	+
13	21	1	1−	+	+	+	+	+	+	0	+	+	0	+	26	102	+
14	24	1	1	+	+	0	0	0	0	+	+	+	0	+	28	102	0
15	25	1	1−	0	+	+	+	0	+	+	+	+	0	0	22	101	+
16	25	25	1	+	+	+	+	+	+	+	+	+	+	+	24	101	0
17	25	14	1	+	0	0	+	+	+	+	+	+	+	0	30	100	0
18	21	8	1	+	+	+	+	0	+	0	+	+	0	+	22	100	+
19	20	1	1	+	+	+	+	0	0	+	+	+	+	0	22	100	+
20	21	4	1	+	+	+	+	0	+	+	+	+	0	+	28	103	0
21	32	2	2−	+	+	+	+	0	0	0	+	+	+	0	24	100	+
22	21	4	1	0	0	+	+	0	0	+	+	+	0	0	24	103	+
23	19	1	1	0	+	+	+	0	0	+	+	+	+	0	26	104	+
24	23	24	1	+	+	+	+	0	0	+	+	+	0	0	24	99	0
25	21	1	1−	+	+	+	0	0	0	+	+	+	+	0	24	99	+
26	40	5	2	+	0	+	+	0	0	0	+	0	0	0	24	101	0
27	23	2	2	0	+	+	+	0	0	+	+	0	0	+	26	103	+
28	20	2	1	0	+	+	0	0	+	+	+	+	0	0	24	97	0
29	26	48	1	0	+	+	+	0	+	+	+	+	0	0	20	101	0
30	19	3	1	+	+	+	+	0	0	+	+	+	0	+	24	101	+
31	19	3	1	+	+	+	+	0	0	+	+	+	0	+	24	101	+
32	21	3	1	+	0	+	+	0	0	+	+	+	0	+	24	101	+
33	19	2	1	+	+	+	0	0	0	+	+	+	0	+	20	100	+
34†	19	1	1	+	0	+	+	0	0	+	+	+	0	+	22	101	+
35	18	1	1	+	+	+	0	0	+	0	+	+	0	+	20	102	+
36	20	10	1	+	+	+	+	0	+	+	+	+	0	0	26	101	+

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carry the meningococcus at the peak of an epidemic and the premise that the elimination of the carrier would terminate an epidemic is entirely theoretical and impractical to effect.

Late in November, 1942 an epidemic of acute respiratory infection had its inception and reached its peak in December, 1942 and the first 3 weeks in January, 1943. The terminal phase of this peak of case incidence coincided with the onset of the meningitis epidemic as indicated in Chart 1. From these observations it seems probable that there was a close association between the epidemic of upper respiratory infection and the epidemic of meningococcal infection. This is contrary to the belief of many epidemiologsts.

Clinical Aspects. The clinical picture presented by patients suffering from meningococcal infections is protean and varies from one of an overwhelming generalized sepsis with collapse, associated with the Waterhouse-Friderichsen syndrome, to that of a mild evanescent type of infection associated with generalized aching, slight aching, slight fever, a few skin lesions, and with bacteremia. As a result of the differences in the clinical features, we have elected to divide our cases as follows: (1) the acute meningococcal septicemia with meningitis (51 cases), (2) acute meningococcal septicemia without meningitis (2 cases) and (3) acute evanescent meningococcemia (8 cases). The last group of cases in contrast to the aforementioned fulminating types are exceedingly mild, and are, as will be shown in another paper, self-limited. It is our opinion from a review of the literature on epidemic cerebrospinal meningitis that the features of those cases with evanescent meningococcal bacteremia have not been sufficiently emphasized.

It is not within the scope of this paper to discuss the signs and symptoms of meningococcal meningitis in detail, however, the essential findings at the time of admission in the cases herein reported are tabulated in Table 1. All of the commonly described signs and symptoms were observed; and, in addition, there was encountered with a striking degree of frequency a sign which the authors have not heretofore seen included in textbooks nor in treatises relating to this disease. In almost all cases (53 of the 61) there appeared an unusual increase in the respiratory rate. In fact, tachypnea introduced a confusing situation in a few cases, without evidence of marked meningeal irritation, in that when it was associated with fever, chill, mild headache, and leukocytosis, pneumonia was simulated. There was no relationship between the height of the temperature and the respiratory rate, since of 10 cases admitted with an average temperature of 98.2, the average respiratory rate was 24.6 per minute.

In this series of 61 cases, at the time of admission, signs and symptoms were observed (see p. 483) in the 51 cases of acute meningococcal septicemia with meningitis and 2 cases of acute meningococcal septicemia without meningitis:

The laboratory data are presented in Table 2. Although meningococci may be recovered from the nasopharynx, the blood, or from the spinal fluid at the onset of meningitis, our bacteriologic study did

not include examination of specimens obtained from the nasopharynx. Of the 51 cases of meningitis, the cerebrospinal fluid was cloudy on admission in 47 cases. In patients Nos. 15, 22, 40, and 42 the spinal fluid contained 64, 22, 8, and 10 cells respectively on admission, but became grossly cloudy and contained 11,700, 14,200, 12,400 and 1,750 cells respectively on the 2nd hospital day. Gram-negative intracellular diplococci were demonstrated in stained smears of the cerebrospinal fluid in 36 cases, or 71% of those in which lumbar punctures were made. From the cerebrospinal fluid, positive cultures of *Neisseria intracellularis* were obtained in 33 cases, a percentage rate of 65. The blood culture was positive in 28 cases (53%) of the patients with meningitis. With direct smear of the spinal fluid, culture of the spinal fluid and the blood culture, laboratory confirmation of meningococcal infection was obtained in 47 cases (90%). In 28 instances meningococci were identified as Type 1. In one case Type 2A was present.

SIGNS AND SYMPTOMS OBSERVED

(The respiratory rate was not recorded in 2 cases)

	No. of cases
Tachypnea	47
Headache	45
Chill (or chilly sensation)	31
Generalized aching	40
Vomiting	38
Arthralgia	13
Nuchal rigidity	46
Positive Kernig	36
Restlessness	21
Apathy	14
Coma or semi-coma	14
Delirium	4
Petechiæ	32
Purpura	4

In view of the fact that demonstration of the organism has been possible in 90% of our cases, a brief description of the cultural methods utilized seems indicated. Details of the method will be published elsewhere.[6]

Blood Culture. Ten cc. of the patient's blood is added to 150 cc. of sterile tryptose phosphate broth. The inoculated flasks are incubated at 37° C. and are observed at intervals for bacterial growth for at least 2 weeks. On occasion, growth has been noted for the first time after 2 weeks.

Spinal Fluid Culture. (*a*) Spinal fluid is inoculated on chocolate blood agar plates, placed in an atmosphere of 10% carbon dioxide and incubated at 37° C. for from 1 to 2 days. (*b*) One cc. of spinal fluid is added to 10 cc. of sterile Bacto-Tryptose-Phosphate broth. (*c*) One cc. of spinal fluid is added to modified Tryptose-Maltose-Carbonate broth. The inoculated tubes are incubated at 37° C. in an atmosphere of 10% carbon dioxide for 1 to 2 days and are observed for bacterial growth.

It is imperative that both the blood and spinal fluid be immediately inoculated into the culture media at the bedside.

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TABLE 2.—SUMMARY OF FINDINGS IN 53 CASES OF MENINGOCOCCAL MENINGITIS*

	Cerebrospinal fluid				Blood				Sulfadiazine therapy				
											1st 5 days		
Patient	Cell count	% polys.	Culture	Smear	Culture	Initial W.B.C.	% polys.	Urine hematuria	Total S.S.D.†	Total S.D.	Total S.D. and S.S.D.	S.D. blood level	Total days treatment
1	9,220	92	0	+	+	13,000	79	0	12 5	76	64 5	24 1	10
2	7,450	93	0	+	+	6,800	65	+	15 0	56	41 0	9 2	17
3	1,880	88	+	+	0	22,700	91	0	15 0	106	75 0	17 4	13
4	995	92	0	+	0	22,000	86	+	8 5	52	60 5	21 5	5
5	2,800	94	+	0	+	12,000	79	0	13 5	43	56 5	17 5	5
6	2,300	98	+	+	0	7,600	57	+	15 0	40	43 0	9 3	8
7	30,000	95	+	0	+	10,900	70	0	5 0	48	39 0	11 8	7
8	44,000	91	0	+	0	14,600	79	0	10 0	106	68 0	13 9	16
9	7,350	98	+	+	+	24,100	77	+	10 0	68	44 0	16 6	13
10	15,400	..	0	+	0	35,000	91	+	13 5	120	75 5	19 5	13
11	5	0	0	0	0	11,700	85	+	20 0	93	62 0	16 8	15
12	13,900	96	+	+	+	13,600	86	+	15 0	66	45 0	17 3	12
13	3,100	94	+	+	+	44,700	83	+	13 5	82	59 5	17 5	11
14	5,600	94	0	+	0	15,200	79	+	23 5	85	66 5	10 5	13
15	64‡	90	+	0	+	24,100	77	0	15 0	60	39 0	13 9	11
16	6,700	89	+	+	+	18,700	81	+	8 5	81 5	58 0	15 8	12
17	17,800	88	+	0	0	10,800	52	+	15 0	76	51 0	16 5	9
18	5,000	95	0	0	0	30,090	87	+	5 0	83	53 0	16 2	10
19	2,850	89	+	+	+	32,700	90	+	13 5	73	69 5	15 3	10
20	3,050	96	+	0	+	31,430	84	+	15 0	65	64 0	21 7	9
21	6,600	87	+	+	+	10,150	61	+	10 0	70	58 0	13 8	10
22	22‡	9	+	0	+	34,500	81	+	10 0	69	55 0	11 9	11
23	1,500	94	+	+	+	15,450	80	+	5 0	68	49 0	12 0	11
24	2,400	95	+	+	+	19,700	83	0	5 0	74	53 0	12 5	11
25	6,850	79	+	+	+	27,100	93	0	5 0	76	58 0	12 0	10
26	12,350	95	0	0	0	14,300	88	0	5 0	68	57 0	12 0	11
27	5,500	88	+	+	0	28,550	95	+	12 5	52	50 5	15 4	9
28	5,800	94	+	+	+	17,900	84	0	10 0	66	48 0	11 7	9
29	1,250	97	+	+	+	16,450	84	0	15 0	52	53 0	11 8	8
30	292	90	+	+	+	25,200	84	+	10 0	80	60 0	12 4	13
31	750	90	+	+	+	23,650	86	+	10 0	72	58 0	13 1	11
32	7,750	97	0	0	0	17,500	93	0	5 0	60	51 0	15 9	8
33	7,750	97	0	+	0	13,400	87	0	10 0	55	61 0	12 4	8
34	22	0	0	0	+	11,000	85	+	10 0	60	50 0	12 4	8

24	2,400	95	+	+	+	19,700	83	0	5.0	74	53.0	12.5	11
25	6,850	79	+	+	+	27,100	93	0	5.0	76	58.0	12.0	10
26	12,350	95	0	0	0	14,300	88	0	5.0	68	57.0	12.0	11
27	5,500	88	+	+	0	28,550	95	+	12.5	52	50.5	15.4	9
28	5,800	94	+	+	+	17,800	84	0	10.0	95	58.0	11.7	9
29	1,250	97	+	+	+	15,450	84	0	15.0	52	53.0	13.8	8
30	202	90	+	+	+	25,200	84	+	10.0	80	60.0	12.4	13
31	750	96	+	+	+	23,650	86	+	10.0	72	58.0	13.1	11
32	7,750	97	0	0	0	17,500	93	0	5.0	60	51.0	15.9	8
33	7,750	97	0	+	0	13,400	87	0	10.0	55	61.0	13.4	6
34	22	0	0	0	+	17,200	84	0	10.0	70	64.0	12.3	10
35	14,200	97	+	+	+	33,600	85	0	5.0	77	50.0	10.5	11
36	5,800	95	+	+	+	17,050	81	0	10.0	82	68.0	13.8	9
37	3,500	96	0	+	+	19,850	68	+	5.0	74	51.0	13.5	10
38	10,000	38	+	+	+	11,650	86	+	5.0	68	55.0	13.8	9
39	11,600	96	0	+	+	19,700	88	+	10.0	44	45.0	17.4	10
40	8‡	0	0	+	0	24,750	91	+	8.0	62	58.0	14.3	6
41	12,000	95	+	0	+	9,650	69	+	5.0	55	38.0	15.6	10
42	10‡	0	0	+	0	16,750	89	+	15.0	70	55.0	14.4	7
43	850	98	+	+	+	36,000	93	+	10.0	57	53.0	17.9	8
44	1,300	95	0	+	0	17,350	84	0	10.0	58	62.0	18.9	6
45	12,950	97	0	0	−	28,550	54	0	§	..	..	..	11
46	4,750	98	+	+	0	26,600	88	0	5.0	68	52.0	21.3	9
47	10,300	93	+	0	0	10,300	93	0	10.0	70	52.0	21.2	8
48	570	50	+	+	0	11,000	78	0	5.0	56	39.0	22.0	9
49	35,700	98	+	+	−	6,500	26	0	§	..	..	..	8
50	8,750	96	0	0	0	18,150	30	0	§	..	..	..	13
51	6,600	97	0	+	0	29,050	89	0	10.0	84	70.0	13.4	9
52	17,550	89	+	0	0	17,850	77	0	5.0	111	56.0	19.6	15
53	1,000	54	+	0	0	17,200	82	0	5.0	57	55.0	14.4	7
Av. or %	9,440	92%	65%	71%	53%	19,768	80	53%	10.0	62.5	55.7	15.2	10

* Cases No. 11 and No. 34 were acute fulminating meningococcal septicemia without meningitis.

† Sodium sulfadiazine; S.D. = sulfadiazine.

‡ Case Nos. 15, 22, 40 and 42 showed 11,700 cells with 91% polys; 14,200 cells with 94% polys: 12,400 cells with 98% polys and 1750 cells with 84% polys on lumbar puncture on second hospital day respectively.

§ 3 infants on whom sulfadiazine levels were not done.

Para-amino-benzoic acid was used for the purpose of inhibiting the action of the sulfadiazine when it had been used in 2 cases prior to obtaining blood and spinal fluid for culture. However, no growth resulted.

Diagnostic Procedure and Treatment. All patients suffering from meningococcal infections should be considered as potentially seriously ill. In order to obviate confusion resulting from a swiftly changing personnel and assist ward officers newly arrived and, therefore, unfamiliar with the hospital routine in dealing with patients suspected of suffering from meningococcal infection, the following outline was prepared:

1. Notify the laboratory that a specimen of cerebrospinal fluid is to be withdrawn by lumbar puncture. The laboratory furnishes:
   (*a*) 1 sterile glass tube with cotton stopper
   (*b*) 1 tube of sterile Bacto-Tryptose-Phosphate broth
   (*c*) 1 tube of modified Tryptose-Maltose-Carbonate broth
   (*d*) 1 chocolate blood agar plate
   (*e*) 1 flask of Bacto-Tryptose-Phosphate broth for blood culture

If the patient has received any sulfonamide the laboratory is notified in order that it should furnish media to which has been added para-amino-benzoic acid.

2. Complete blood count is requested.

3. Urine specimen to be obtained if patient can void.

4. Directions for lumbar puncture. This procedure will not be initiated until the specimen tubes and media arrive from the laboratory. Strict surgical asepsis will be carried out. The fluid will be permitted to escape slowly. Allow 10 to 15 drops to fall directly into each of the 2 test tubes containing the broth media, 5 drops on the blood agar plate and about 5 cc. into the empty sterile test tube.

If the spinal fluid is cloudy, or if in the opinion of the medical officer the patient is suffering from a meningococcal septicemia, the following therapeutic procedure will be immediately instituted:

5. Five gm. of sodium sulfadiazine are dissolved in 100 cc. of sterile distilled water and injected slowly intravenously, using a salvarsan set. If the patient is unconscious a second 5 gm. of sodium sulfadiazine will be given 8 hours later.

6. Sulfadiazine, 2 gm. every 4 hours. Start the oral medication upon completion of the injection of sodium sulfadiazine.

7. One hour after the administration of sodium sulfadiazine 1000 cc. of 5% glucose in physiologic salt solution will be given intravenously.

8. Sufficient fluid intake by mouth or/and intravenously will be administered to secure a minimum daily output of urine of 1500 cc.

9. For 5 days daily determinations of the blood concentration of sulfadiazine will be made and every 48 hours thereafter as long as the patient is receiving the drug.

10. White blood counts and differential counts will be made every other day as long as the patient is receiving the drug and twice weekly throughout the period of hospitalization.

11. The blood concentration of sulfadiazine will be maintained at a level of 12 mg. per 100 cc. for 5 days.

12. Urinalysis will be made every 2nd day.

13. A culture of the nasopharynx for meningococci will be made 3 days prior to the expected date of discharge.

Sulfadiazine and sodium sulfadiazine were the sole chemotherapeutic agents used in all cases with the exception of Cases 12, 14, and 15, which were given in addition to chemotherapy, 30 cc., 30 cc., and 90 cc. of polyvalent meningococcus antiserum, respectively. It was believed that no favorable response resulted from the use of antiserum in Cases 12 and 14 and in Case 15 the response was equivocal.

Sulfadiazine and its sodium salt appeared to effect a cure in all cases. Both drugs were used in all cases with the exception of the 3 infants. The initial intravenous dose of sodium sulfadiazine was 5 gm. and the average total dose of this drug was 10.01 gm. Fourteen of the cases received only 5 gm. but 11 required 15 gm. or more because of persistent vomiting or the failure of the sulfadiazine blood level to rise adequately early in the course of the disease. The total amount of sulfadiazine administered orally varied considerably. The average total dose was 62.5 gm.; the minimal amount was 40 gm. and the maximal amount was 120 gm. Our observations lead us to believe that most of the cases had practically recovered by the 6th hospital day. The study by Banks[2] of spinal fluid taken 12, 24, and 48 hours after the diagnostic puncture, demonstrated that bacteriostasis was effected in 24 hours, that phagocytosis of free organisms had taken place and that within 48 hours the process of absorption of the exudate was well advanced when sulfathiazole was used. In view of these observations and in the light of our own clinical observations, an analysis of the amount of sulfadiazine and its sodium salt given and the sulfadiazine blood level determinations during the first 5 hospital days seems warranted. The amount of *sodium* sulfadiazine has already been noted and these figures will not be repeated since all of this drug was administered during the first 5 days of hospitalization. The amount of sulfadiazine given orally varied from 24 gm. to 66 gm., with an average amount of 44.6 gm. However, the minimum total amount of sulfadiazine and its sodium salt was 38 gm., the maximum was 75.5 gm. and the average was 55.7 gm. during the first 5 days of treatment. The blood sulfadiazine level was obtained almost daily for 5 days on all cases. In some instances when the blood level was unusually high or low, a second determination was made the same day. The lowest average blood level was in Case 2, 9.2 mg. per 100 cc.; the maximum was in Case 1, 24.1 mg.; and the average for the first 5 day period for all cases was 15.2 mg. The total number of days of treatment varied from 5 to 17; in 62% of the cases the therapy was given for a period of 10 days or less. The average for all cases was 10 days.

Only 1 serious complication, namely agranulocytosis, was encountered as a result of sulfadiazine therapy. This occurred, perhaps by coincidence, in Case 10, who had received the largest dose of sulfadia-

zine of any patient in this series. The white blood count fell from 4600 on the 15th hospital day to 1950 with only 8 neutrophils on the 19th hospital day. However, improvement began 5 days later and he made a slow recovery following the use of blood transfusions, pentnucleotide and adenine sulfate.

Hematuria was noted in 53% of the cases, the cause of which was attributed to the large doses of sulfadiazine. However, gross hematuria was noted in only 3 cases and in no instance did anuria or other serious renal complications occur. Sulfacrystalluria was observed in 9 cases.

The symptomatic treatment did not vary from that which has been recommended by others with the exception that we have used morphine rather freely for the control of severe headache and extreme restlessness when bromide and chloral or barbiturates did not succeed in controlling these symptoms.

We encountered 2 patients in whom acute meningococcal purulent arthritis was a complication. This complication will be dealt with in another communication.

Discussion. Factors that are responsible for converting the carrier into the disease state are still unknown. However, it is interesting to note that in 68% of our cases, a history of an antecedent upper respiratory infection was present and that the onset of the meningitis epidemic followed the peak of a severe epidemic of upper respiratory infection. It is obvious that the disease is not highly contagious, since in no instance was there evidence of cross-infection.

Although it is customary and required to assess the severity of the disease at the time of admission, we feel strongly that every case should be regarded as potentially seriously ill. The picture of a "mild" case of meningococcal meningitis characterized by headache, slight fever, generalized aching, and nuchal rigidity in an individual who does not appear severely ill can change so rapidly into a comatose or semi-comatose patient with generalized purpura, convulsions, and extreme collapse that an evaluation of their status at the time of admission is of no consequence.

On admission the clinical features of meningitis were similar in most cases and occurred in the course of, or following, an acute respiratory infection. Notable exceptions were in the following: Patient 52 complained of left lumbar pain of such severity that he was surveyed temporarily, but briefly, on the urologic service for a suspected urinary calculus. The chief complaint of Patient 8 was severe epistaxis, and in Patient 34 the swollen, painful joints were conspicuous features. The coexistence of contagious diseases is rare, but in Patient 48 meningitis and mumps with probably mumps encephalitis occurred. On admission he had severe bitemporal headache and nausea for 36 hours; except for pharyngeal mucosal injection and suggestive nuchal rigidity, the physical examination was negative. The white blood cells numbered 11,000 with 78% neutrophils. On lumbar puncture the cerebrospinal fluid was grossly clear but contained 570 white blood cells with 50% neutrophils and 50% lymphocytes. The following

morning bilateral parotitis developed. At this time a second lumbar puncture was done. The spinal fluid contained 232 white blood cells, 77% of which were neutrophils. This case occurred during a period when mumps was prevalent. That mumps encephalitis coexisted in this patient seems highly probable in view of the fact that the differential spinal fluid count showed 50% lymphocytes, an observation noted in only 1 other apparently uncomplicated case. Fortunately, a stained smear of the spinal fluid on admission was positive for gram-negative intracellular diplococci.

A study of these 53 cases, together with the 8 cases of evanescent meningococcal bacteremia to be reported elsewhere, makes it evident that the pathologic evolution of the disease is characterized by an initial infection in the nasopharynx following which the organisms migrate to the blood stream. From the blood, invasion of the tissues results. That meningitis is not an invariable occurrence as a sequel to meningococcal bacteremia is evident, since in 4 of the aforementioned 8 cases the etiologic agent was not discovered for from 3 to 6 days following the time of admission and at the time the patients were recovering from their untreated bacteremic disease. Although the symptoms and findings in the nervous system tend to obscure other focal manifestations of septicemia, more emphasis should be placed on the latter to facilitate earlier recognition and the institution of treatment before meningitis ensues.

No time should be lost in instituting immediate chemotherapy in large doses. From the reports in the literature, we have the impression that many of our cases could have been successfully treated by giving the drug by the oral method without resorting to the intravenous method. Nevertheless, there are many advantages in initiating the therapy by the intravenous method. A few hours of valuable time is gained since it is now generally accepted that the drug given by mouth is absorbed rather slowly and is not followed by a rapid rise of the drug content in the blood. The importance of obtaining a high blood level of sulfadiazine early in the course of treatment of pneumonia has been clearly shown.[6] To obtain a high blood level quickly, requires the use of sodium sulfadiazine administered intravenously. The average sulfadiazine blood level taken within 8 to 12 hours following the intravenous injection of 5 gm. of sodium sulfadiazine and a variable amount of peroral sulfadiazine (from 2 to 6 gm.) was 13.3 mg. per 100 cc. The results obtained with the combined intravenous use of sodium sulfadiazine and the peroral use of sulfadiazine have led us to conclude that this method is therapeutically effective and is the treatment of choice in meningococcal infections.

Summary and Conclusions. An epidemic of 61 meningococcal infections occurred following a wave of acute respiratory infections. The latter seemingly bore a direct relation to the onset and progress of the epidemic of meningococcal infections. Eighty-six per cent of the cases developed among raw recruits.

In 51 cases of acute meningococcal septicemia with meningitis and 2 cases of acute fulminating meningococcal septicemia without men-

ingitis, all of the commonly described signs and symptoms were encountered, but in addition to these findings, tachypnea was noted in 88% of the cases.

The initial treatment should routinely consist of sodium sulfadiazine intravenously and repeated in those cases where the oral administration of sulfadiazine is not feasible. There were no fatalities among the 53 cases reported in this series and the additional 8 cases of acute evanescent meningococcal bacteremia to be reported also survived.

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BURN TRAUMA PRECIPITATING ACUTE LEUKEMIA OR A LEUKEMOID CONDITION

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The subject of the interrelationship of trauma to acute myelogenous leukemia poses an interesting problem. Recently, a patient under treatment on our surgical service for extensive burns suddenly presented the picture of a blood dyscrasia, which terminated fatally.

It is difficult to evaluate the wide variety of opinions of the factors involved in the possible etiology of acute leukemia. Before attempting to do so, it is important to consider whether the disease is of infectious or neoplastic origin. MacCallum[11] presented the view that acute leukemia has the appearance of an acute infectious process, wherein one finds hemorrhages, and necrotic and ulcerative stomatitis as a common occurrence. Sternberg[16] suggested that myeloblastic leukemia be separated from the other leukemias, and be regarded as purely infectious in nature; since the pathologic picture is so striking in similarity to infection, moreover some severe infections cause the appearance of numbers of myeloblasts and myelocytes. Hirsch[8] concluded that infection plays a major rôle in the etiology of all cases of acute leukemia. The basis for this belief is that acute myelogenous leukemia is associated with fever, toxemia, chills and other manifestations of an infection. In addition, infections are often associated with this blood dyscrasia.

Many maintain the opposite view. Piney[14] concluded that leukemia is a neoplasm. Dimmel,[5] and likewise DeCastello,[4] stated that the

leukemic process was not an infection and could not be identified with sepsis. The feeling was that a process that spreads and involves other organs forming hematogenous metastases cannot be regarded as hyperplastic but rather as neoplastic. Likewise, Cecil[3] preferred that leukemia be catalogued in the category of neoplasias rather than that of infections, maintaining that it is a fatal invasive pathologic process. True, up to the present time, against the infectious theory for acute leukemia are the facts that no organism has been recovered, the disease has not been reproduced experimentally, and the disease has not been transmitted from one animal to another.

It is evident from the foregoing that no conclusion as to the validity of either theory can be made. However, a number of authors have reported cases wherein the occurrence of trauma preceding the onset of leukemia has possibly been more than a coincidence. Rubnitz[15] offered the possibility that splenic trauma may cause acute myelogenous leukemia. Olovson[13] collected 67 cases wherein leukemia occurred in association with trauma to the spleen and long bones. His discussion did not include cases of rupture of the spleen which were pathologic complications of leukemia. Lewson[10] conceded that trauma to the hemolytopoietic organs does not always cause leukemia; but believed that in individuals with an inherent predisposition, leukemia may first appear following such trauma. The relationship seems analogous to that of special kinds of trauma in the production or stimulation of sarcomas and carcinomas. On the other hand, Ewing tended to exclude trauma as a possible causative factor in leukemia.

Yaguda and Rosenthal[18] have cited the criteria as set down by Liniger which would establish the corelationship between trauma and leukemia. In essence they do not differ from those proffered by Olovson; namely, that the individual must have been free of disease symptoms prior to the trauma, a suitable severe injury must have occurred, and a lag period must elapse between the injury and the disease.

In the literature, apparently, trauma to the long bones with or without fracture, trauma to the spleen or splenic areas with or without rupture, or trauma which causes severe generalized body concussion, have been the only types of trauma suggested as possible etiologic factors in leukemia. The case we are reporting is one in which a picture quite similar to that of myelogenous leukemia appeared shortly after a severe cutaneous burn.

Case Report. *History of Present Illness.* A soldier, age 28, black, was admitted to the hospital on August 21, 1943. On the morning of admission, the soldier had lit a gasoline field stove preparatory to cooking breakfast. The flame was so excessive that he was unable to reach the valve to diminish it. When attempting to sprinkle sand on the burner, the gasoline tank of the stove exploded showering the soldier with burning gasoline. The blaze was smothered by wrapping him in blankets.

Past and Family History. Past history gave no indication of any previous physical abnormalities or hint of any disease process either acute or chronic. There was no contributory family history.

Physical Examination. The soldier appeared his given age and was well developed and well nourished. He was in apparent shock on admission, which

was 1 hour after the accident. There was wide distribution of burned areas—second, third and fourth degree—of the forehead, face, both ears, both shoulders both forearms and hands, both lower extremities from ankles to groins. The estimated surface area of burn was calculated according to Berkow's method[1], to be approximately between 55 and 60%. Pulse on admission was 120, and blood pressure 122 systolic and 72 diastolic. Other physical findings were essentially negative.

Laboratory Data. On admission, the blood count was normal, 4,800,000 R.B.C., 85% hemoglobin, 12,000 W.B.C. (69% neutrophils, 25% lymphocytes and 6% monocytes). The hematocrit was 59% (Hayden's method). Urinalysis: specific gravity of 1.028, amber color, acid reaction, an occasional R.B.C. Sedimentation rate was 1 mm. (Cutler).

Treatment and Progress. Shock therapy was instituted in accordance with accepted authorities. One-half grain of morphine sulfate was administered hypodermically. During the first 24 hours 3000 cc. of plasma was infused. The burned areas were quickly and carefully débrided under aseptic precautions. Within the second 24 hours, 1350 cc. of plasma and 3 cc. of adrenal cortex in divided doses was given, followed on the 3d day by 650 cc. plasma and 2 cc. adrenal cortex. The fluid intake *per os* was augmented by infusions of either glucose-saline or glucose-water combinations.

The condition of patient was progressing satisfactorily. Sulfadiazine in small doses was administered as a precautionary measure against infection. The burned areas epithelized rapidly. The soldier was taking nourishment well and was mentally alert.

CHART I.—ILLUSTRATING PERIPHERAL BLOOD PICTURE ON VARIOUS DAYS OF ILLNESS

Date	R.B.C.	Hgb.	W.B.C.	Seg.	Juvenile stabs	Metamyelocyte	Premyelocyte	Myeloblast	Myelocyte	Eosinophil	Basophil	Lymphocyte	Monocyte	Normoblast	Hematocrit	Remarks
8/21/43	4.78	85	12,150	63	6							25	6		59	
8/22/43	4.24	85	16,650	62	8					1		20	9		55	
8/25/43	3.82	70	14,500	66	5					1	1	21	6		39	
8/28/43	2.68	65	50,200	50	35		1		4			8	2		30	Toxic granules in neutrophils
8/29/43	2.42	60	65,300	37	41		5	3	1	1		9	3	6	30	Macrocytosis, polychromatosis
8/30/43	2.21	55	88,500	50	20	7	4	3	2			10	4	10	28	"
8/31/43	2.68	55	83,200	42	28	5	1	4	7			9	4	5	30	"
9/ 1/43	2.51	60	81,000	23	38	2	9	6	6	1	1	11	3	9	28	"
9/ 2/43	2.46	55	137,000	34	32		4	9	4		1	13	3	5	28	"

BONE MARROW STUDY

Date	Myeloblasts	Premyelocyte	Myelocytes	Juvenile Stabs	Polys.	Monos.	Eos.	Macroblasts	Normoblasts
9/2/43	76	3	11	6	2	1	1	15	21

On the 8th day of his illness, there was a decided alteration in his blood picture (Chart I), though clinically his general condition seemed to be progressing favorably. This was the initial indication that, regardless of his apparent improvement, something radical was occurring in his hemolytopoietic system. From the 9th day to his death on the 13th day, his condition rapidly deteriorated despite treatment. On the 11th day after admission the soldier was restless and desired to get out of bed. The following day he appeared brighter and more coöperative. During the morning of the day of his death, he became noisy and unmanageable, finally going into a coma 2 hours before termination. Several blood transfusions were given, but the reaction of the hemolytopoietic system was irreversible. The white cell count of the peripheral circulation, prior to death, had reached a level of 137,800 (including 4 myelocytes, 4 premyelocytes and 9 myeloblasts). Towards the end of the case, a bone-marrow study revealed 76% myeloblasts, 3% premyelocytes, 11% myelocytes, 2% segmented neutrophils, 6% juvenile and stab forms, 1% monocytes and 1% eosinophils.

Necropsy. The findings were very meagre. The lungs were not involved in any pneumonic process, the arteries and veins contained blood in which the erythrocytes were reduced in number. However, the white blood cells were numerous and displayed a mark shift to the left. There was nothing noteworthy in the heart, aorta, gall bladder, brain and adrenals. Cloudy swelling (albuminous degeneration) was noted in the liver, spleen, kidneys, lungs and pancreas. The spleen was only slightly enlarged. Damage to the hemolytopoietic system was evidenced throughout with a decided shift of the granulocytes to the left.

Discussion. The case presented is that of a young man, who up to this accident was apparently healthy, carrying on the normal arduous duties of a soldier with complete satisfaction to his superiors. In the $1\frac{1}{2}$ years of his army career, this was his only hospitalization. On his admission to this institution, his blood picture was normal; as time progressed his burned areas were healing satisfactorily, and then when recovery was in the offing, his blood picture became chaotic. One may or may not be inclined to ascribe this solely to a leukemoid reaction, which Krumbhaar[9] first described some years ago; wherein, in some extreme infections and a few other conditions, one may find huge numbers of myeloblasts, myelocytes and neutrophils circulating in the blood, only to disappear as the infection clears. Again, Goldbloom *et al.*[7] reported cases of leukemoid reactions caused by sulfapyridine, but here one must keep in mind the possible effects of the benzene ring drugs. Likewise, Moody and Knouf[12] cite similar occurrences which were alleviated by blood transfusions. However, in our case there was no appreciable infection, and furthermore, the injury to the hematopoietic system was so great that the reaction was irreversible.

Stitt *et al.*[17] asserted that leukemia is often a perverted response to the stimulus of infection and often cannot be differentiated sharply from cases with leukemoid reaction. Consequently, the question arises—where do leukemoid reactions end and leukemia begin? Of course if one accepts leukemia as neoplastic, then, as there is a great variety of carcinogenic stimuli, the differentiation is difficult and must depend on the course of the case. If the patient recovers, and the blood picture reverts to normal, then one may justifiably assume that the condition was that of a leukemoid reaction. However, if the patient presenting no manifestations of other disease processes fails to recuperate, and the blood maintains its perversion as the only major pathologic finding, then it is difficult to accept this irreversible reaction as one of the leukemoid type.

True, as mentioned, the spleen in our case was only slightly, if at all, enlarged. However, in acute leukemia, as Boyd[2] stated, the spleen may be of almost normal size.

The pertinent contribution of this case is the possible etiology in relation to the burns. According to the criteria as set down by Liniger and also by Olovson, the necessary criteria were present for citing this case as one of traumatic leukemia. All cases previously reported have had an interrelationship of injury either to the spleen or long bones and leukemia. As far as we know, this is the first time where an extensive burn is offered as the possible cause of leukemia. However, this is not wholly the contention of the authors. Of course, one may contend

that this patient, if he had lived long enough, without trauma, might have developed leukemia in any event. We feel that if this patient had so-called latent leukemia, the burn might have served as a "catalyst" in hastening the manifestation of the leukemic process.

Summary. 1. The evidence as to the infectious or neoplastic nature of acute myelogenous leukemia is discussed.

2. Evidence and opinions are cited holding trauma to be a possible etiologic factor in acute leukemia.

3. A case of an extensive burn which terminated with a picture stimulating acute leukemia is presented.

4. The opinion is offered by the authors that trauma, in our case specifically a burn, may be a precipitating agent in the production of leukemia.

We hope that this paper will stimulate further investigation. The relationship of burn trauma to leukemia requires considerable clarification. Also, the question arises whether those patients who have recovered from so-called leukemoid reactions will, if experiencing again with some severe infection or trauma, exhibit once more a tendency toward a perverted blood response.

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USE OF AN AGGLUTINATION-INHIBITION TEST IN STUDYING AN EPIDEMIC OF INFLUENZA

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The first well-described European influenza epidemic occurred in 1510;[9] however, it was not until 1933 that the virus etiology of this disease was firmly established by Smith, Andrewes and Laidlaw.[10]

Until very recently, the laboratory confirmation of a clinical diagnosis of influenza could be undertaken only at highly specialized centers. In 1941, a simple test for detecting influenzal antibodies was introduced by Hirst.[5] Now this confirmation can be attempted by clinical laboratories.

During December, 1943, and January, 1944, there was a marked increase in the incidence of respiratory diseases among the military and civilian population of the West Coast of the United States. Clinically most of these were diagnosed as influenza. To aid in its investigation of this epidemic, the Virus Section of the Ninth Service Command laboratory employed a modification of the Hirst test.

The test depends upon the fact that red cells of certain fowls and mammals are agglutinated by both influenza Type A and Type B viruses, and that convalescent human sera specifically inhibit this agglutination. It is therefore referred to as an Agglutination-Inhibition (A-I) test. The technique found to be most satisfactory in this laboratory was based on one described by Burnet.[3]

Material and Methods. *Collection of Specimens.* Samples of blood were drawn from patients in the "acute" and "convalescent" phases of influenza by the medical and laboratory staffs of the several stations studied. The serum was separated from the clotted blood, and submitted to this laboratory in vials containing small amounts of sulfanilamide as a preservative.[4] Prior to testing, the sera were kept at ice-box temperature.

Equipment. Flat-bottomed Kolmer racks, Kahn test tubes, 1 ml. serologic pipettes and a water-bath regulated to maintain a temperature of 56° C. were used.

Chicken cells. These were obtained every other day from a local poultry market at the time of slaughter. Blood from the neck veins of single birds was collected in approximately 3 times the volume of 2% sodium citrate. It was immediately filtered through several thicknesses of gauze. The cells were washed twice in 0.9% saline and finally centrifuged at 1500 r.p.m. for 10 minutes. From these packed cells a sufficient amount of a 1.5% suspension was made in 0.9% saline for each day's run. The remaining cells were stored in the ice-box and rewashed before using. They could be kept for several days without seriously interfering with the test.

Virus Suspension. Allantoic fluids containing Type A (PR-8) and Type B (Lee) strains of influenza virus were used. They were prepared by inoculating 10 to 12 day embryonated chicken eggs by the allantoic route with 0.1 ml. of a 10^{-2} or 10^{-3} dilution of virus. After 40 to 48 hours of incubation at 36° C., the eggs were placed in the ice-box and the following morning the allantoic fluid was harvested. An average of 7 ml. were obtained from each egg. Agglutination titers of 1 to 320 or above were considered satisfactory. The fluid was frozen in CO_2 awaiting use, however, even at ice-box temperature a workable titer of the virus could be maintained for several weeks. A titration of each virus and a check on the unitage of the prepared suspensions were done each day before starting the tests. To 0.1 ml. of allantoic fluid, 0.9 ml. of saline was added to make a 1 to 10 dilution. Thereafter twofold serial dilutions were made with 0.5 ml. of saline going out to 1 to 2560 (9 tubes). To each tube, containing 0.5 ml. of diluted allantoic fluid, 0.25 ml. of the chicken cell suspension was added. The tubes were shaken a few times by hand and allowed to stand for 1 hour at room temperature. The last tube in which the sedimented red cells did not run on tilting was considered the agglutination end-point. Since in the actual Agglutination-Inhibition test, 8 "agglutinating units" of virus were used, this titer (original dilution) was divided by 8 and a suspension of that strength prepared. After 20 minutes at room temperature the strength of this suspension was checked. To 0.5 ml. of the diluted sus-

pension, 0.5 ml. of saline was added, and twofold dilutions using 0.5 ml. of saline were made. Only 4 dilutions were necessary. To each tube, 0.25 ml. of the chicken cell suspension was added. The tubes were then shaken a few times by hand and read after 1 hour. If exactly 8 "agglutinating units" were not present in the prepared suspension, appropriate adjustments were made by adding more of the allantoic fluid containing concentrated virus or of saline.

Serum. Each specimen of serum was inactivated and serially diluted before testing. To do this 0.125 ml. of serum was delivered into a Kahn tube which was then corked and placed in the 56° C. water-bath for ½ hour. Next, 0.875 ml. of saline was added and twofold dilutions made with saline ($\frac{1}{8}$ to $\frac{1}{1024}$). This dilution was made in the first of 2 parallel rows of Kahn tubes, and as it progressed 0.25 ml. of each dilution was delivered to the appropriate tube in the second row. When completed there were 2 rows of test tubes each containing 0.25 ml. of serially diluted serum.

The Agglutination-Inhibition (A-I) Test. Acute and convalescent phase sera from a patient were always tested at the same time in order to avoid variation in behavior of the reagents.[6] To each tube, containing 0.25 ml. of a serum dilution prepared as in the preceding paragraph, there were added 0.25 ml. of a virus suspension of 8 "agglutinating units" (Type A in the front and B in the rear row) and 0.25 ml. of the 1.5% suspension of chicken cells. The tubes were shaken by hand a few times and then allowed to stand at room temperature for 1 hour. The end-points were read as the original dilution of the serum in which agglutination of the chicken cells by the respective viruses was completely inhibited. Included in each series of tests were Type A and B virus controls in which saline was substituted for the 0.25 ml. of serum, a cell control in which 0.25 ml. of the cell suspension was added to 0.5 ml. of saline, and a serum with a known high agglutination-inhibition (A-I) titer for each of the influenza types. No increase or a single tube increase in the agglutination-inhibition (A-I) titer of a convalescent over an acute phase serum was reported as "negative." An increase of 2 or more tubes (fourfold) was reported as "positive."

Problems Studied and Results. An attempt was made to type all the sera submitted with this Agglutination-Inhibition (A-I) test. The results were then analyzed. The A-I antibody response of individuals to influenzal infection, as well as the overall statistical picture and the epidemiologic tendencies were studied.

During the epidemic, sera from 119 patients clinically diagnosed as suffering from influenza were examined. They came mostly from two stations in central coastal California (Table 1).

Forty-nine of these patients showed a fourfold or greater rise in A-I antibody for influenza Type A. One had such a rise for Type B as well. Because of the unusual nature of this response, sera from this individual were sent to Dr. M. D. Eaton of the United States Army Board for the Investigation of Epidemic Diseases for retesting. He confirmed the rise in antibodies for both Type A and Type B influenza. Similar observations were made by Lennette *et al.*[8] in the 1941 epidemic, using a complement-fixation technique.

Even though it was soon apparent that the epidemic was due to a Type A virus, all specimens submitted on patients diagnosed as having influenza were tested against both types of virus. This was done in order that any changes in the influenzal pattern might be detected. A few sera from individuals with atypical pneumonia were also tested without revealing evidence of recent influenzal infection.

TABLE 1.—DISTRIBUTION OF CASES OF "INFLUENZA" TYPED BY AGGLUTINATION-INHIBITION TEST

Period	Station 1		Station 2		Station 3		Station 4		Total cases studied	Positive (%)
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.		
Before Dec. 5	..	..	0	1	..	..	..	..	1	0
Week of Dec. 6	0	1	0	5	..	..	..	..	6	0
Week of Dec. 13	10	17	5	4	..	..	..	..	36	42
Week of Dec. 20	14	10	2	3	..	..	..	..	29	55
Week of Dec. 27	6	4	3	2	..	..	..	..	15	60
Week of Jan. 3	5	7	1	0	..	..	..	..	13	46
Week of Jan. 10	0	5	..	..	1	3	1	1	11	18
Week of Jan. 17	0	5	..	..	..	..	1	1	7	14
Week of Jan. 24	0	1	..	..	..	..	..	..	1	0
	35	50	11	15	1	3	2	2	119	41

Not infrequently, the interval between the 2 specimens submitted on each patient was only 2 to 3 days. It was therefore apparent that the earliest and shortest interval in which a rise in antibody could be expected would have to be determined. To obtain this information the results of testing 108 patients were examined on the basis of the

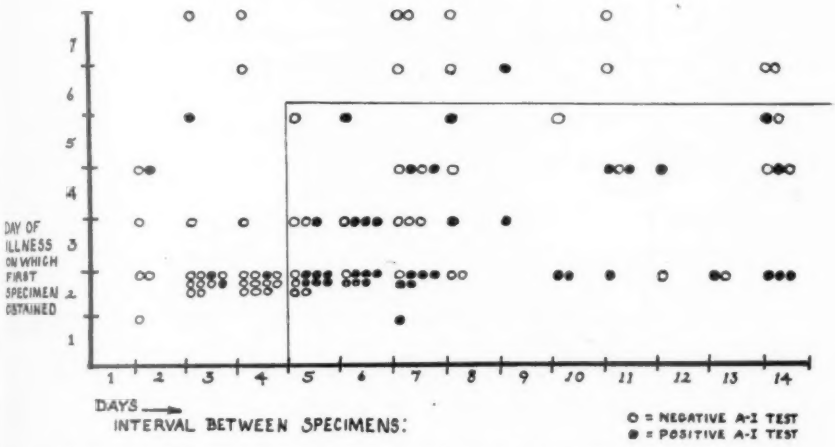


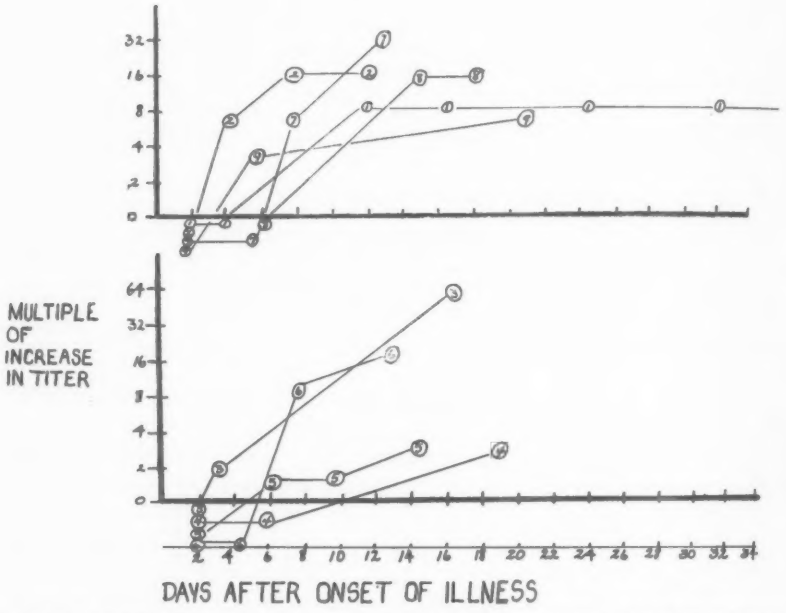
CHART 1.—Relation of day on which specimens collected to type of reaction.

day after onset on which the first specimen was collected and the interval between specimens (Chart 1). A large number of these individuals showed a definite rise in antibody by the end of the first week. There were 65 patients from whom the first specimen of serum was obtained within the first 5 days after onset of the illness, and a convalescent one after an interval of at least 5 days. Among this group, 62% had an influenzal disease which could be typed, in contrast to the 41% among the entire group of patients.

In Graph 1 curves are drawn for 9 patients from whom it was possible to obtain 3 or more specimens. It is apparent that the A-I antibody curve continues to rise after the 1st week. In 2 individuals (4 and 1) who were available for "check-up," antibody levels were

maintained after 6 and 9 weeks, respectively. The different manner in which individuals react to a clinically similar illness is also demonstrated by this graph.

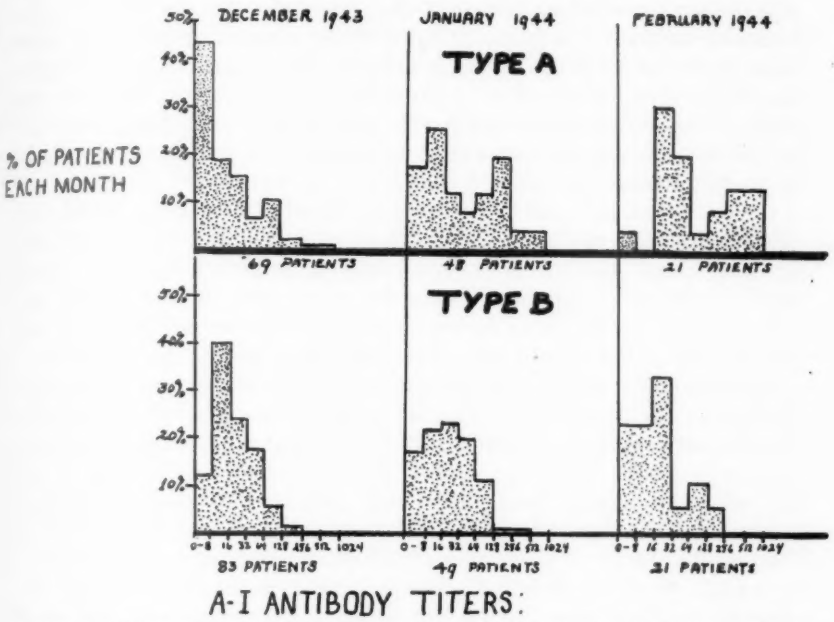
The highest incidence of cases which could be typed occurred during the last days of December, 1943 (Table 1). This was the period during which the epidemic reached its peak in this region. Since there is great individual variation in the so-called "base line" level of A-I antibody of "normal" individuals (1/4 to 1/1028), it is impossible to determine evidence of infection in a patient from a single specimen. However, when the "base line" levels are adjusted on the basis of overlapping known positive sera, to account for variation in reagents due to tests being done on different days, a very definite trend is



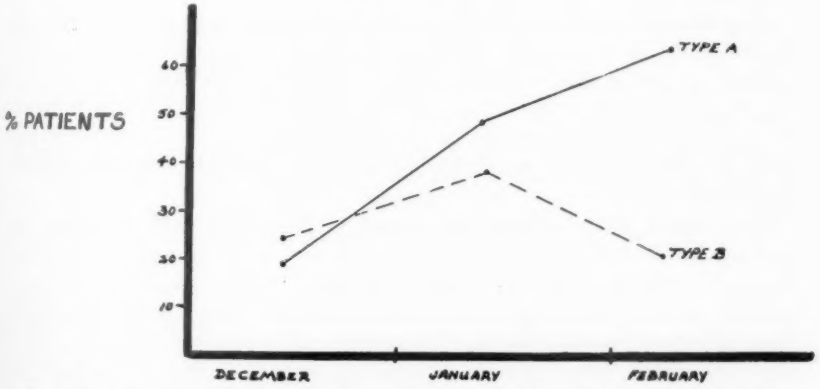
GRAPH 1.—Development of agglutination-inhibition (A-I) antibody for influenza Type A (in 9 patients).

noted as the epidemic subsided. In Graph 2 sera from patients in the acute stages of illness are grouped on the basis of adjusted levels of A-I antibody to influenza Types A and B. These sera were all collected during December, 1943, January and February, 1944. Type A titers are shown for 138 patients and Type B for 153. The smaller number in the former group is due to the fact that in some instances there were no satisfactory overlapping Type A sera. Consequently some of the early determinations could not be adjusted to the sensitivity of those done in later weeks. Although the number of specimens in the third period is considerably smaller, it is apparent that as the influenza epidemic subsided there was a tendency for the A-I antibody level for Type A influenza to rise, while that for Type B remained

essentially unchanged (Graph 3). During these later weeks the laboratory confirmations of influenza were very few.



GRAPH 2.—Effect of Type A influenza epidemic on agglutination-inhibition antibody levels of acute sera.



GRAPH 3.—Per cent of patients each month whose acute sera had corrected A-I titers for influenza Types A and B of 1 to 64 or above.

Discussion. The A-I antibody determination has a number of distinct advantages over the several other methods now available for measuring antibody changes associated with convalescence from influenza. Although no 2 of these tests give entirely concordant results, the A-I antibody more closely parallels the neutralizing antibody than does the antibody detected by the complement-fixation technique.[2] Per-

formance of this test is also much simpler than is a complement fixation, *in vivo* mouse or egg neutralization. It can be done by any trained laboratory technician. Since guinea pig or human "O" cells may be substituted for chicken cells,[11] all the materials necessary for its performance are available in most clinical laboratories, except for the virus. This might be furnished by large central laboratories since the agglutinating ability of the fluid containing virus has been shown to be stable at ice-box temperature for several months.[1] Consequently the laboratory confirmation of a clinical diagnosis of influenza may easily be made routine.

It is appreciated that there are difficulties associated with the test due to variations in cells, virus and human "base line" levels.[6] Testing both acute and convalescent specimens at the same time avoids many of these. Using the known positive serum in an overlapping manner makes possible an estimation of the relative sensitivity of the test on different days so that comparative studies may be made.

The technique used in this laboratory is not original, but is especially adapted to the facilities of a clinical laboratory. The reading of type of sediment rather than density of supernatant is more practicable in laboratories where a photoelectric densitometer is rarely available.[7] The use of 8 "agglutinating units" of virus permits easier reading of end-points, though it may decrease somewhat the sensitivity of the test. The small volumes of each reagent which go into the test make for a saving of materials without any appreciable decrease in accuracy. The use of a live virus does not present any great danger as the likelihood of accidental laboratory infection with these "derivative" strains[3] is slight.

The importance of proper spacing of specimens is apparent when the incidence of 41% positive reactors obtained when all specimens submitted are compared with the 62% resulting when only those with a satisfactory interval are taken. It would appear that if the first specimen of blood is drawn when a patient is first seen and the second at least 1 week later, the greater percentage of A-I antibody rises would be detected.

The failure of 38% of the influenza convalescents, with satisfactorily spaced specimens, to show evidence of a rise in antibody to either Type A or Type B influenza is of interest. Although a few of these individuals had such relatively high initial antibody levels that slight rises might not have been easily detected, the majority did not. They may represent individuals who have an especially high threshold for producing A-I antibody, or instances of an etiologically different, but influenza-like disease. The one man who developed an increase in A-I antibody to both Type A and Type B influenza virus suggests either a double infection or more likely an anamnestic reaction with Type B antibody. No instances of Type B infection alone were detected in the group.

From an epidemiologic point of view the cases studied were rather unique. They all occurred in previously healthy young men of military age. The greater proportion of cases came from a post which received

men newly inducted from civilian life in that area. They probably reflected the situation in the surrounding civilian community. The next largest group were aviation cadets who had been in the Army for a much longer time. No striking difference was apparent in the response of these 2 groups to the disease. The highest percentage of positive reactors occurred during the 3 weeks at the peak of the epidemic.

The sera represented in Graphs 2 and 3 reflect the influenza agglutination-inhibition (A-I) antibody status of a group of soldiers at the onset of the illness responsible for hospitalization. Most of these patients had probably been exposed to the epidemic of Type A influenza during December and early January. It is therefore significant that their "base line" levels for Type A influenza A-I antibody tended to rise as the epidemic subsided, while those for Type B remained unchanged.

Summary. 1. An epidemic of influenza in several army installations was studied by using an influenza Agglutination-Inhibition (A-I) test.

2. The technique of the test which is modified for use in larger hospital laboratories without special equipment or personnel is presented.

3. One hundred and nineteen clinically typical patients were studied. Of these, 49 (41%) were found to have developed a rise in antibodies to influenza Type A and one to Type B as well.

4. The importance of proper spacing of acute and follow-up sera is shown. The incidence of positive reactors rose to 62% when only those patients from whom a first specimen was taken within 5 days of onset and a second after an interval of at least 5 days were considered.

5. The highest percentage of positive reactors occurred at the height of the epidemic. As the epidemic subsided, the average "base line" level of A-I antibody for Type A among sera submitted for study tended to rise.

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XUM

EXPERIMENTAL CHRONIC CARBON MONOXIDE POISONING OF DOGS*

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The existence of a definite state which may be characterized as chronic carbon monoxide poisoning has not been established. One view of the situation has been summarized by Drinker[6] as follows: "There can be no doubt that when people breathe small amounts of carbon monoxide daily over weeks and months of time they may suffer ill-health. But the degree of ill-health is variable. . . . . " The clinical signs and symptoms of chronic carbon monoxide (CO) poisoning reported in the literature are unfortunately indefinite and uncharacteristic. A further difficulty in evaluating the above quoted statement arises in determining what is actually meant by "small amounts." Bulletin 3 of the U. S. Department of Labor (1941) sets the limit of safe concentration of CO in air in industrial plants at 0.01 vol. % (100 p.p.m.), based upon the report of Bowditch et al.[4] These values should not be used without reservation. It is well known that occasional short periods of seriously increased gas concentration are hard to avoid in industry and often pass unobserved unless continuous records are kept. If this occurs, the situation changes at once from chronic mild CO intoxication into the range of repeated acute poisoning. A second complication in the problem lies in the evident fact that we are interested primarily in the quantity of CO in the body (measured in per cent of carbon monoxide hemoglobin, [HbCO]) and only secondarily in the amount available in the atmosphere. The actual amount of CO combined with hemoglobin is given only in a few publications, and has been found to vary greatly, even in the same garage.[11] Workers may move from regions of extreme exposure to places with low CO concentration. Examinations by Killick[10] have suggested that an individual exposed continually for some months to the same CO concentration in air may, supposedly by adaptation, show a gradual decrease in the percentage of COHb. Hence, safety limits given in terms of CO concentration in air give only an approximate and perhaps unreliable idea of the toxicity relationships of the gas in the body.

The above value of 0.01 vol. % CO in air leads theoretically in man to approximately 16% COHb (calculated, using the value of 210[13] for K in the equation $K = [HbCO] .p [O_2] / [HbO_2] .p [CO]$). By agreement of the Safety Engineers of the U.S.A.,[2] the upper permissible limit is set at 20% HbCO. These data are based on Haldane's recom-

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

mendation to the London Underground Railways in 1897.[9] One attempt only, so far as we know, has been made to study experimentally whether these figures are innocuous for exposures of months under conditions which actually occur in industry. The results of this study by Suepfle, Hofmann and May[14] are equivocal.

It seemed of special interest in these times of industrial man-power shortage and in view of the fact that there are situations in the Army where routine exposure to sufficient CO occurs to allow formation of 20% HbCO to make a careful study of the effects of chronic exposure to comparable amounts of carbon monoxide. Dogs were chosen as the experimental animals, as continuous exposure over long periods was desired and since in this species also exposure to 0.01 vol. % CO leads to approximately 20% HbCO.

Technique. Six dogs were exposed for 11 weeks, from April 27 to July 13, 6 days a week, with a mean period of exposure of $5\frac{3}{4}$ hours per day, to an atmosphere of approximately 0.01 vol. % CO in the air. A seventh dog was later added to the group so as to observe the effect of the same amount of CO upon an animal whose heart had been damaged, 1 year prior to the present experiment, by means of ligation of the posterior coronary artery. This animal was exposed for 18 days only, and sacrificed 3 months later.

CO Chamber. A controlled flow of compressed air was fed into the chamber to which an initial single amount of pure CO was added. Subsequently a constant amount of 15 mg. pure CO per minute was fed into the air stream with the help of a motor-driven pump. The actual air concentration in the chamber was measured hourly by means of the CO determinator of the Mine Safety Appliance Company (MSA). The MSA apparatus was controlled by use of the iodine pentoxide method and calibrated with the help of gas mixtures of known concentration. Blood of at least 3 dogs within the chamber was withdrawn at the end of the daily exposure and the HbCO content as well as total pigment determined.

The mean (M) of all *CO determinations* in the air showed that the concentration of the gas was maintained at 0.0096 ± 0.00065 (SD) vol. %. The standard error (SE) of the mean was less than $\frac{1}{100}$ of the mean. The mean of all HbCO determinations in the 6 animals after daily exposure was $20.1 \pm 1.1\%$ (SD), with an SE_M of ± 0.15. The mean difference of the HbCO determinations from dog to dog on each single day was 1.1%.

Determination of HbCO and Total Hb. HbCO and total pigment were determined spectrophotometrically. The analyses were upon the blood samples diluted 1 to 100 with water. For a description of the spectrophotometric technique, readers are referred to Drabkin and Austin.[5] In our hands the spectrophotometry has been found to have advantages of accuracy and directness over gasometric methods in determination particularly of mixtures of pigments.[3] Special details in the technique as applied to mixtures of HbO_2 and HbCO will be presented elsewhere.

The dogs used in the study were kept long enough in our kennels to convince us of their freedom from acute diseases, especially distemper. None of the dogs showed any sign of disease during or after the experiment.

Results. The *condition* of all the animals appeared excellent during the whole experimental period.

Temperature, pulse and respiration of all the dogs were taken before the daily exposure and in some at the end of the afternoon, and did not vary beyond usual normal limits. *The body weight* increased in most of the animals during the first weeks of the experiment and remained stable thereafter. The dietary ration was a mixture of

natural foodstuffs, presumably complete in all essentials. At the end of the experimental period all the animals appeared well nourished. All dogs were of friendly *disposition* at the beginning of the experiment and remained so throughout the whole period. They did not become unduly excited or quiet at the end of the single day of exposure nor at the end of the whole experiment. Even temperatures up to 102° F. in the chambers had no apparent effect, except in 1 dog, made somewhat ill for 1 or 2 days.

Electrocardiograms obtained from the dogs showed changes in the 2nd week of the experiment in 1 animal, and in the 10th week in another. These findings are discussed in detail in a separate paper (Ehrich, Bellet and Lewey[7]). They were interpreted as evidence of permanent myocardial damage. The electrocardiographic changes persisted until the animals were sacrificed 3 months after termination of the experiment. At necropsy the hearts of the 4 dogs which were available for examination showed degenerative changes of individual muscle fibers. A close correlation was found between the electrocardiographic and the morphologic changes.

Periodic *neurologic examination* of all animals revealed almost negligible clinical signs. In 1 dog the pupillary reaction to light decreased, in another the knee jerks became more active, the hopping reaction became poor in 2 dogs, the placing in 3 and jumping in 1 animal. Walking on the fore- or hindlegs when the opposite extremities were supported became difficult or impossible in 4 animals. The dogs showed a tendency to stand and walk on a broad basis, stiff and slightly atactic. No changes were seen in the electroencephalogram or on the part of the peripheral nerves.

The HbCO of the 6 dogs was determined at different times in the morning before the beginning of the exposure, after having been gassed the previous day for 7 hours each and having reached 20% HbCO. In none of the animals could any HbCO be detected. This would appear to support Drinker's opinion that the average values of 2.11% HbCO found by Farmer and Crittenden[8] in workers 16 hours after exposure were the consequence of smoking on the way to work rather than of delayed elimination.

Morphologic Examination of the Nervous System. The central nervous system of 5 of the 6 dogs exposed to 0.01 vol. % CO in air for a period of 11 weeks, 6 days a week, with a mean exposure of $5\frac{3}{4}$ hours per day, leading to not more than 20% HbCO in the blood at any time, showed distinct histopathologic changes 3 months after termination of the exposure. These changes differed quantitatively from those found in acute CO intoxication, but were qualitatively of the same type and showed the same predilection for certain regions of the brain.

No alterations were found in the *peripheral nerves.*

All animals showed some indication of *cortical damage* of varying type. Figure 1 illustrates a typical wedge-shaped infarct within which the nerve cells of the external granular and pyramidal layers are sclerosed, pyknotic and shrunken. In other instances, the degenerations within the cortex are so diffuse that a dense glia carpet in the

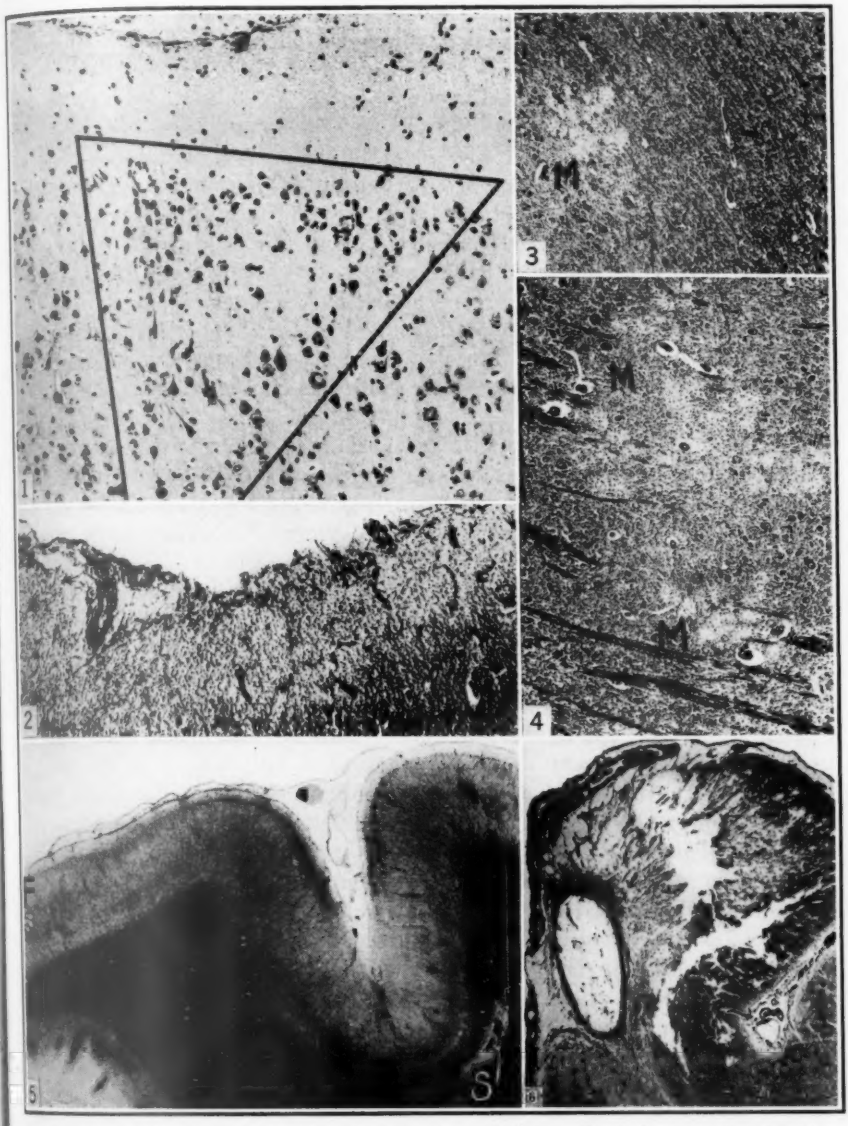


FIG. 1.—Wedge-shaped focus in the cortex in which the cells of the second to fourth layer are pyknotic and shrunken. (321.) (Cresylviolet, × 120.)

FIG. 2.—Dense layer of marginal glia fibers formed on one side of the calcarine fissure. (749.) (Phosphotungstic acid, × 150.)

FIG. 3.—Minute foci of necrosis (mottling) in the cortex (*M*). (737.) (Phosphotungstic acid, × 70.)

FIG. 4.—Minute foci of necrosis (mottling) in the lateral thalamic nucleus (*M*). (749.) (Phosphotungstic acid, × 70.)

FIG. 5.—Cavity formation in the cortex (*F*) and in the white matter (*S*) of F_3. (321.) (Weigert, × 10.)

FIG. 6.—Large cyst formation within necrotic area of frontal lobe. (737.) The cyst is walled off by a connective tissue capsule which is surrounded by a glia capsule. (Laidlaw's silver impregnation, × 30.)

superficial cortical layers is the sole sign of cortical disintegration (Fig. 2). In 1 dog a spongy degeneration of all layers of a convolution resembles closely the appearance of the cortex as seen in severe anoxia through occlusion of the pial vessels.

The mildest form of this "anoxic necrosis" is expressed in form of "mottling" of the cortex (Fig. 3) or of the lateral thalamic nucleus (Fig. 4), *i. e.*, minute foci of disintegration in which myelin, axis cylinders and ground substance alike have broken down and are so completely cleaned out that not even a scar has been formed. Small cavities are the only indication of the degeneration of the parenchyma. In the dog with preceding cardiac operation (321), stasis in the cortical blood-vessels clearly played a dominant rôle, producing grapelike cortical cavities (Fig. 5), whereas the large subcortical foci are probably true necroses rather than the consequence of vascular obliteration.

Occasionally both the superficial vascular system of the pia and the deep system of the large ascending arteries of the circulus arteriosus seemed to be involved. In these instances a whole convolution or a greater part of it became necrotic to the degree of forming large cysts (Fig. 6). Their anoxic origin is still evident from the fact that the scar in the white matter surrounding the cyst is purely gliotic, whereas the immediate capsule of the cyst as well as the repair of the cortical necrosis are of mesodermal nature.

The involvement of the long arteries of the white matter is clearly manifest in the large and small foci of softening in the *white matter*, prominently in the occipital lobes (Figs. 7 and 8) and in the dissolution of the U fibers (Figs. 9 and 10), which as a rule belong to the most resistant structures of the brain but were reported as involved in acute CO poisoning by Meyer.[12] In a milder form of vascular impairment patches of perivascular gliosis in the white matter (Fig. 11) or small softenings in the nuclei of the brain stem (Fig. 12) are indicative of the damage produced.

Of most significance are the changes in the *basal ganglia* which, though of minor severity, are more frequent in these chronic than in acutely poisoned animals which we have studied. Here again all gradations are seen. Demyelination of the fibers in the capsula externa, the putamen, the external and internal medullary bundles, as well as of the thick fibers in the globus pallidus proper seem to characterize the earliest signs (Figs. 13 and 14). Loss of axis cylinders in the same bundles suggests a more advanced process (Figs. 15 and 16). In 1 animal a circumscribed but complete softening in the most medial and anterior part of the globus pallidus was found along the course of an artery, the walls of which were necrotic (Fig. 17). The focus is so neatly cleaned out that it may be inferred that it had appeared several weeks prior to death.

Discussion. The clinical signs in 7 dogs which had breathed an atmosphere of 0.01 vol. % CO for 5½ hours a day, 6 days a week, over a period of approximately 3 months were not impressive. But they were, nevertheless, slightly less vague than symptoms and signs de-

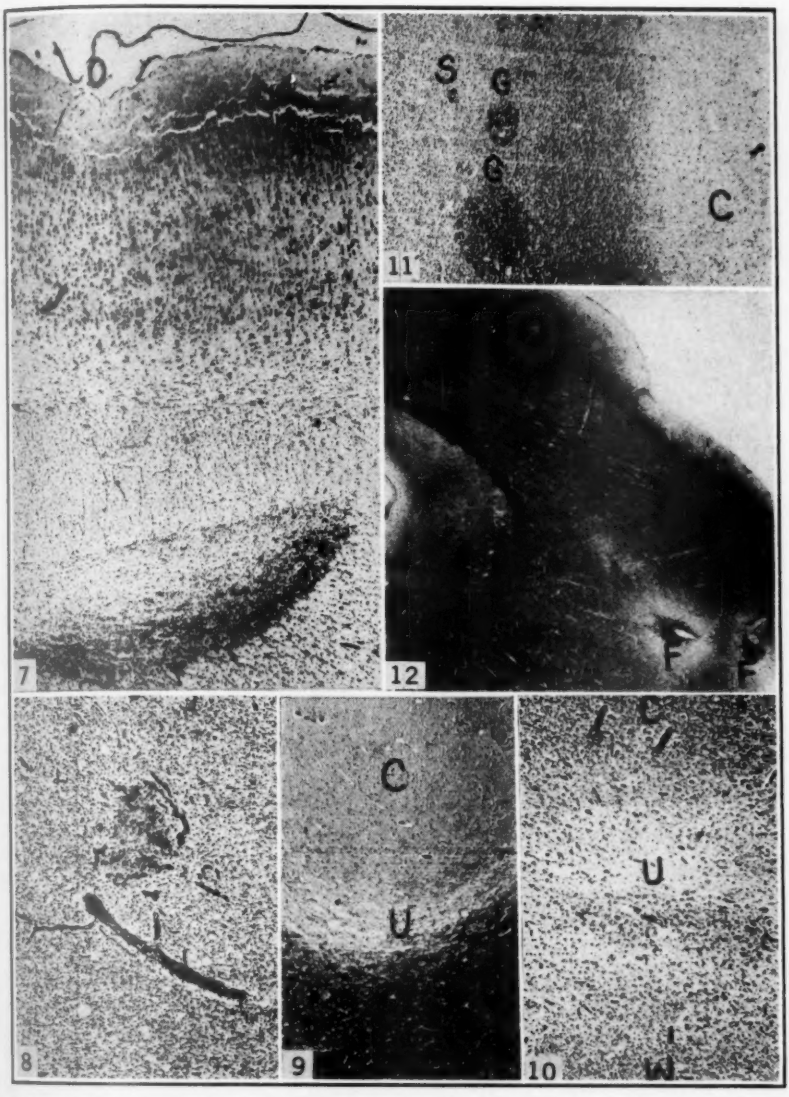


FIG. 7.—Large softening with reparatory sprouting of capillaries in the occipital lobe. (749.) (Cresylviolet, × 30.)

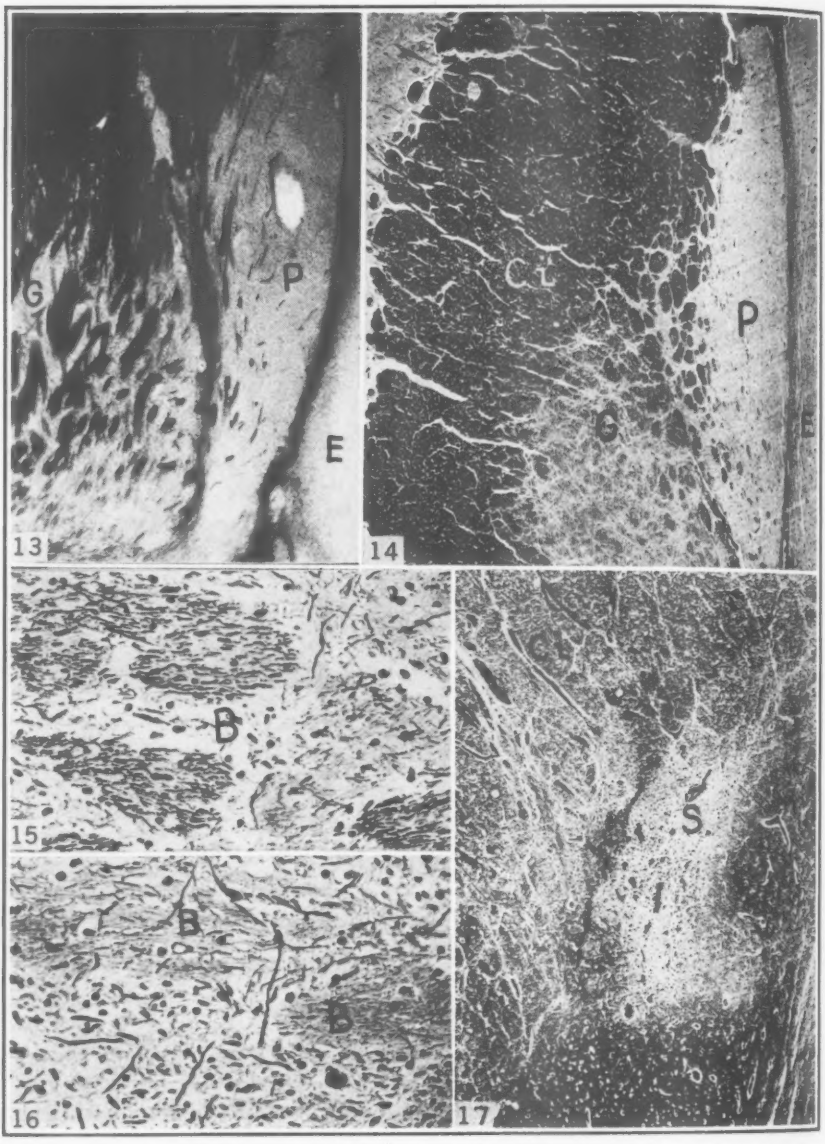
FIG. 8.—Small focus of disintegration with connective tissue scar in connection with proliferated blood-vessel in occipital lobe. (321.) (Laidlaw's silver impregnation, × 70.)

FIG. 9.—Loss of U fibers (*U*) below cortex (*C*). (739.) (Phosphotungstic acid, × 30.)

FIG. 10.—Loss of U fibers under higher power (*U*). Cortex (*C*). White matter (*W*). (739.) (Bodian axis cylinder staining, × 70.)

FIG. 11.—Softening (*S*) and foci of perivascular gliosis (*G*) in the occipital lobe underlying the cortex (*C*). (737.) (Phosphotungstic acid, × 30.)

FIG. 12.—Foci of softening and cavity formation (*F*) in the corpus geniculat. med. and the lateral lemniscus. (321.) (Weigert, × 10.)



FIGS. 13 and 14.—Putamen (*P*) and globus pallidus (*G*) in the same magnification (×20). Figure 13, a normal control dog; Figure 14, chronic CO_2 dog (737) Ci. capsula int. E. capsula externa. The loss of medullated fibers in putamen, globus pallidus and laminæ medullares is evident. (Weigert: myelin sheaths.)

FIGS. 15 and 16.—Shows cells and fiber bundles of the globus pallidus with axis cylinder impregnation. Figure 15, a normal control dog; Figure 16, a chronic CO dog (739). Figure 15 shows large nerve cells and dense bundles of axis cylinders (*B*), whereas the nerve cells in Figure 16 are shrunken and the bundles (*B*) void of axis cylinders except for one in the right lower corner. (Bodian axis cylinder impregnation, × 330.)

FIG. 17.—Large focus of softening along necrotic blood-vessel in the most anterior and medial part of the globus pallidus. *S*, softening; *Ci*, internal capsule. (746.) (Laidlaw's silver impregnation, ×30.)

scribed as characteristic of chronic CO poisoning in man. It may be worthwhile to check whether the anomalies of gait and posture, which represented the only constant findings in these dogs, may also be found in man after chronic exposure to CO.

The disposition of all our dogs remained friendly. Suepfle *et al.*[14] observed that their dogs became irritable and easily frightened towards the end of their experiment of 13 weeks' duration. This psychic reaction disappeared after termination of the intoxication. Hence, workers came to the conclusion that the exposure of dogs to 0.01 vol. % CO, even over several months, failed to produce any clinical signs while 0.02 vol. % represented for dogs the limit of tolerability because of the described psychic changes. However, Suepfle and colleagues report that exposure to 0.01 vol. % CO for 5½ to 6 hours daily led in their dogs to only 7% HbCO and exposure to 0.02 vol. % CO to only 13% HbCO. These findings appear incomprehensible to us, since our animals invariably reached values of 20% HbCO in exposure to 0.01 vol. % CO. The results of Suepfle *et al.* are therefore difficult to interpret.

The clinical findings in our dogs were too uncharacteristic to be of any value were they not confirmed by mild but definite histologic changes in the hemispheres, basal ganglia and the stem of the brain. There is no doubt that type and localization of the histologic alterations in the brain of the chronically intoxicated animals, including their strange predilection for the anterior part of the globus pallidus are identical qualitatively with those seen in acute CO poisoning. The difference between the histologic changes in acute and chronic CO poisoning appears to be purely quantitative. The chronic foci are more scattered, the lesions smaller, and the axis cylinders in them often preserved.

The presence of the histologic changes which have been described in the brain of all 5 dogs available for histologic examination and their absence in all controls, kept upon the same diet and under the same living conditions, leaves little doubt that they have to be considered as due to chronic CO intoxication.

It should not be inferred that similar changes need be expected in the human brain under the same conditions.

No data concerning histologic examinations of the nervous system in chronic CO poisoning of man or animals could be found in the literature. However, one may speculate that similar changes might be detected also in man if the brains of individuals who had survived subacute or chronic CO poisoning without having shown marked or persistent clinical signs were available for examination. It is well known that at necropsy numerous cortical and subcortical foci may be found in man after lethal subacute CO intoxications, although the clinical signs and symptoms had been vague and inconclusive. In addition, Alexander[1] has demonstrated that extensive thromboses of both globi pallidi may not be followed by their clinical equivalent, Parkinsonism, until 15 years after intoxication with carbon monoxide.

Our dogs showed the same value of 20% HbCO after 13 weeks of

exposure as that found after the 1st day of gassing. Thus, there was no evidence of acclimatization to CO in our experiments, as has been reported.[9,10]

Finally, Drinker's[6] question as to the response of the damaged heart to CO may be answered tentatively. The animal in which the posterior coronary artery had been ligated 1 year prior to the chronic CO intoxication showed by far the earliest and severest pathologic changes in both the heart and brain. We do not wish to overemphasize the outcome of this experiment upon one animal, but the result is suggestive.

The implication of the present findings with respect to chronic CO intoxication in man is uncertain, but one fact seems to stand out, namely that 0.01 vol. % CO leading to 20% HbCO is not innocuous for the heart and central nervous system of dogs.

Summary. 1. Dogs, exposed for 5½ hours per day, 6 days a week, over 11 weeks, to an atmosphere containing 0.01 vol. % CO, and reaching daily 20.1 ± 1.1% HbCO, showed a consistent disturbance of postural and position reflexes, and of gait.

2. Some of them showed a pathologic electrocardiogram, characteristic of anoxia, and necrosis of single heart muscle fibers.

3. Their central nervous systems showed, 3 months after termination of the experiment, histologic changes in the cortex and white matter of the cerebral hemispheres, in the globus pallidus and the brain stem. These alterations corresponded in type and localization to those found in acute CO poisoning, but were smaller, more scattered and less destructive. They followed in their arrangement the course of blood-vessels, the walls of which were damaged only occasionally.

4. One dog, in which the posterior coronary artery had been ligated 1 year prior to the exposure for a period of only 18 days to CO, showed the earliest and severest cardiac and cerebral changes of all animals observed. This result suggests that an inadequate functioning heart increases the general risk in CO poisoning, and may be responsible for a higher degree of brain damage.

5. Our findings indicate that chronic CO intoxication may occur in dogs at CO concentrations which have been regarded as being within the safety limits for man.

6. These experiments do not permit any conclusions as to the potential reactions of the human body to the same conditions.

We wish to express our appreciation to Lt. Col. Theodore F. Hatch, Sn.C., of the Department of Industrial Hygiene, for his technical advice in the arrangement of the experiments, to Dr. William Ehrich of the Department of Pathology and Dr. S. Bellet of the Cardiac Department of the Hospital of the University of Pennsylvania for their coöperation, and to Mr. Richard Faber, now a senior in the School of Veterinary Medicine, and Miss H. Lorraine Leidy for valuable technical assistance.

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CARDIAC CHANGES FROM CO POISONING*

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WHILE cerebral lesions from CO poisoning have been repeatedly described, the cardiac changes are not generally recognized. Thus, Drinker[10] has recently stated that there seems to be no definite pathologic evidence of serious cardiac damage in CO intoxications except in the severest degrees of poisoning; in fact, Stearns, Drinker and Shaughnessy[30] have reported that even in lethal doses marked changes in the electrocardiogram may be missing. In view of these and similar statements, we wish to present some observations made during an experimental study of CO poisoning in dogs which seem to indicate that the heart is frequently involved in CO poisoning, and that the cardiac changes are more severe than previously realized.

Literature. Cardiac involvement in CO poisoning was first noted by Klebs.[20] Clinically, he recorded acceleration, and later irregularity and retardation of the heart beat; anatomically, he observed punctiform and diffuse hemorrhages into the pericardium and endocardium, including the tips of the papillary muscles. In at least 1 case he found fatty dystrophy of the myocardium. The clinical observations of Klebs were confirmed by Zondek,[33] Killick,[19] and others, and subsequent writers added to the picture changes in the electrocardiogram such as alterations of the T waves and the S-T segments as well as the symptoms of stenocardia.[8,21,24] The anatomic findings of Klebs were amplified by Liebman,[25] who seems to have been the first to observe myocardial necrosis in CO poisoning. These findings were

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later corroborated by Herzog,[16,17] who observed necrosis and fatty dystrophy in the papillary muscle of the mitral valve, in the apex of the heart, and elsewhere in the left chamber in 14 out of 16 patients; while Gey[11] found hemorrhages especially in the apex of the papillary muscle of the mitral valve, fatty dystrophy of the myocardium, and occasional circumscribed necroses in 9 out of 19 patients. Similar observations have since been reported by several other writers.[12,13,21,32]

Although efforts to induce cardiac changes in experimental CO poisoning were not successful in the hands of some investigators,[25,33] Haggard[15] found in dogs occasional ventricular extrasystoles, inversion of T waves, and heart block; Campbell[5] in a few animals noted marked fatty dystrophy of the myocardium; and Christ[7] in rabbits observed negative T waves and broadening and depression of the R-T segment, as well as subendocardial necroses, especially at the base and apex of the left papillary muscle. No hemorrhages were seen in these experiments.

For the sake of completeness, it should be mentioned that some authors claim to have observed extensive capillary thrombosis of the myocardium,[2] but the evidence presented appears to us insufficient.

Material and Method. All experiments were performed upon stray dogs which were quarantined for a few days to determine their freedom from disease such as distemper. Some experiments represent acute CO intoxication, others chronic poisoning.

In the acute experiments Nos. 238/I, 246, 249, 256, 258, 324, 368, 388, 450, 473 and 615, the animals were allowed to inhale the CO. In some of these, the dogs were connected by a tracheal cannula to a 2-liter rubber bag into which pure O_2 was delivered. The expired air passed through an externally cooled canister filled with soda lime before returning to the bag. Into this closed system freshly prepared CO (96%) was fed in varying quantities and at various intervals. In other experiments of this series a bell-jar was placed over the head of the dog and fixed, by means of a rubber collar, around its neck. Compressed air, the flow of which was controlled by means of a flow-meter and to which 15 cc. of CO per minute were added by a motor driven pump, was fed into the bell-jar and allowed to leave at the collar. In 3 animals of this first series (Nos. 238/I, 368, 388), CO_2 accumulated within the closed system because of an error in technique. Three dogs (Nos. 246, 256, 258) with acute circulatory failure were kept alive by transfusion with about 250 cc. of dog's erythrocytes suspended in an amount of saline solution just sufficient to permit injection.

In a second series of acute experiments (Nos. 198, 233, 238/II, 239, 267) CO was administered by way of intravenous injection of erythrocytes 96% saturated with CO outside the body.

In a series of chronic experiments (Nos. 737, 739, 740, 749) the dogs were exposed in a closed chamber to CO for $5\frac{3}{4}$ hours a day, 6 days a week, over a total period of 11 weeks. The concentration in the chamber was sufficient to obtain about 21% COHb. It amounted to 0.01 vol. % CO, a dose generally regarded as non-toxic.

The dogs Nos. 696, 738, 741, 743, 744 and 745, finally, were placed in a chamber in which the O_2 of the breathing air was reduced to 10 vol. % leading to a partial O_2 pressure in the blood similar to that of 21% COHb. This was continued for $4\frac{1}{2}$ hours a day, 6 days a week, over a total period of 11 weeks.

Two of the acutely poisoned dogs died at the end of the experiment, obviously from the experimental procedure (Nos. 238/I and 239). Two others died after 4 days because of gas infection (No. 256) and confluent broncho-

pneumonia (No. 388). The remaining acute animals were sacrificed at intervals from 4 days to 2 months, some by bleeding, others by air embolism.

The chronic animals were allowed to live for 6 to 7 months after the onset of the experiments, *i. e.*, 3 months after termination of the CO poisoning or the O_2 deficiency. Most of these animals were killed by bleeding.

The organs studied include brain, heart, lungs, liver, kidneys, spleen, intestine, adrenals and lymph nodes. The findings of the brain will be presented elsewhere (by F. H. L.) and therefore will not be discussed here.

Results. *General Observations.* Ten of our animals showed granulomata due to parasites in various organs including lymph nodes, kidneys, lungs, liver, spleen and pancreas; but only 2 showed granulomata in the heart (Nos. 368 and 745). Two dogs harbored tapeworms in their intestines; 2 had Gandy-Gamma bodies in their spleen, and 3 foci of old pyelonephritis and calcified casts in their kidneys. Only 1 animal showed indication of preëxisting more severe disease, namely marked prominence of the juxta-glomerular apparatus of the kidneys as well as hypertrophy of the heart (No. 368).

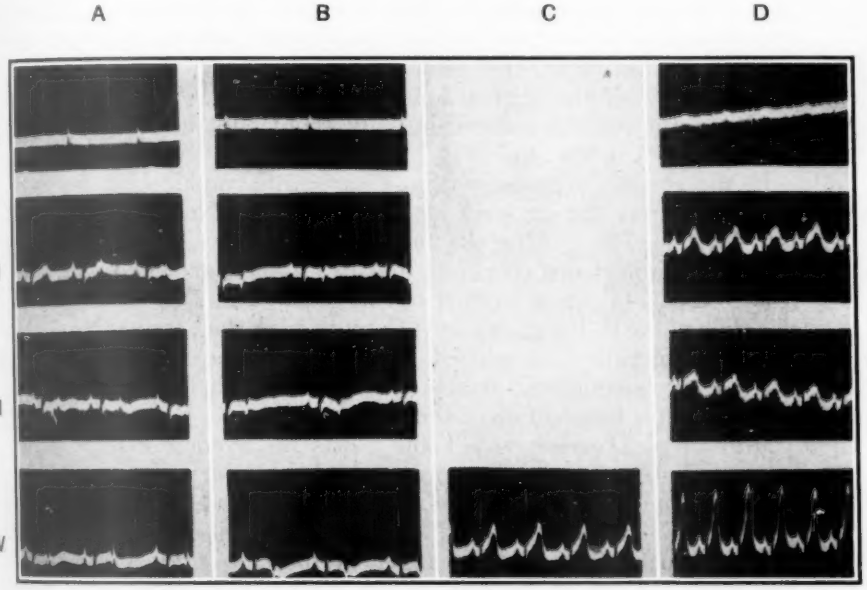

FIG. 1.—Electrocardiograms of Dog 473. Acute experiment, CO inhalation. (*A*) Control 7 P.M. Leads I, II, III and CRIV; (*B*) 8:25 P.M. 40% COHb. Note the sharp T wave inversion in Leads II and III and elevation of T in CR 4 with inverted T waves and sharp downward dip. (*C*) Lead CRIV, 8:51 P.M. 67.5% COHb. Note upright T wave with slight RT elevation. (*D*) 9:35 P.M. 79.5% COHb. Note RT elevation in Lead II, tall T wave in CRIV and presence of tachycardia. Ventricular rate is 200 per minute.

Electrocardiographic Observations. The earliest electrocardiographic change observed in an acute experiment (No. 473) at a COHb level between 40 and 50% COHb consisted in a decrease of the T wave (Fig. 1). The T wave became diphasic and sometimes negative at 70%, and permanently negative when COHb increased from 70 to

75%. After respiration had stopped, and artificial respiration and blood transfusion were administered, the electrocardiogram showed a 2:1 atrioventricular block and a negative T wave as well as an elevation of the R-T segment. The block disappeared within 24 hours, but the T wave remained negative until the animal was sacrificed 4 days after the experiment.

In the 2 animals of our second series which were transfused with erythrocytes saturated with CO, and which were studied electrocardiographically (Nos. 238/II and 239), the sole change in the electrocardiogram consisted of an inversion of the T wave. The highest COHb level obtained in Dog 238/II was 72 to 74.4% for 15 minutes; in Dog 239 it exceeded 75% for 45 minutes and reached 84.4 to 85.6% for 10 minutes. However, the number of erythrocytes in the circulation was doubled in Dog 238/II and increased 6.6 times in Dog 239, which means that the oxygen combining power at this time was considerably higher than would appear from these percentages. In Dog 238/II, for instance, the CO-free hemoglobin did not amount to 25.6 to 28% of the original quantity, but, since the number of erythrocytes was doubled by transfusion, this dog had more than 50% of the original amount of CO-free hemoglobin. Similarly, Dog 239 had as much as 95% of the original amount. Obviously, then, the oxygen combining power was reduced by only about 50% in 1 dog and not more than 5% in the other.

In the chronic experiments, no electrocardiographic changes were observed during the 1st week of the experiment (Nos. 737, 738, 739, 740, 741, 744, 745). After the 2nd week the T wave became negative in 1 CO poisoned dog (No. 739) and in 1 animal under decreased O_2 tension (No. 745) while another of this group (No. 738) developed an elevation of the R-T segment. At the 10th week the CO dog (No. 737), previously negative, developed an inverted cone-shaped T wave. These changes continued unabated until the animals were sacrificed 3 months after termination of the experiment.

Morphologic Observations. Table 1 lists the average *weights of the hearts* and other organs often involved in circulatory disturbances in all of our animals except Nos. 256 and 388, which died from intercurrent diseases, No. 368 which suffered from cardiorenal disease, and No. 744 of which no body weight was taken at the end of the experiment. The heart weights of the dogs in the chronic CO experiments were slightly greater than those of our non-fatal acute experiments. This is in accord with the observations of Campbell,[6] who found a considerable increase in heart weight in mice which were exposed to chronic CO poisoning for 9 months. This was explained by an increase in viscosity of the blood owing to the increase in red cells. The increased heart weights which were found in our fatal acute experiments were probably the result of passive congestion.

Concerning the other organs, it can be learned from Table 1 that the lungs were enlarged in the 2 fatal experiments, and this increase amounted to 4 times the normal weight in No. 239, the blood volume of which had been augmented 6.6 times. The kidneys were enlarged

in our non-fatal transfusion experiments as well as in both fatal experiments, while the spleen was enlarged in the non-fatal transfusion experiments, but not in No. 239. The changes in the fatal inhalation experiments seem to be explained by circulatory failure, while those in the fatal and non-fatal transfusion experiments appeared to be partly caused by the introduction of the large quantities of blood. The failure of enlargement of the spleen in No. 239 was due probably to the early death of this animal, the death occurring at a time when as previously observed[1] the spleen was contracted as a result of acute oxygen want.

TABLE 1.—THE RELATIVE WEIGHTS $\left(\frac{\text{organ weight, gm.}}{\text{body weight, kilo}}\right)$ OF HEART, LUNGS, LIVER KIDNEYS AND SPLEEN IN OUR VARIOUS EXPERIMENTS

	No. of dogs	Average weights				
		Heart	Lungs	Liver	Kidneys	Spleen
Non-fatal Experiments						
Inhalation of CO, acute	7	7.85	9.50	32.2	5.20	2.1
Transfusion with COHb, acute	4	7.70	9.70	28.0	6.15	3.6
Inhalation of CO, chronic	4	8.70	9.05	30.4	4.40	2.0
O_2 deficiency, chronic	5	8.20	11.60	31.6	5.10	2.2
Fatal Experiments						
Inhalation of CO, acute	1	8.80	16.10	37.6	7.00	3.3
Transfusion with COHb, acute	1	9.60	40.70	30.4	7.10	2.1

The *gross appearance of the hearts* was essentially normal in all our chronic experiments and in the non-fatal acute experiments except in No. 473 which was studied electrocardiographically (see page 513) and sacrificed 4 days after the poisoning. In this animal we found extensive subendocardial hemorrhages throughout the left ventricle with special involvement of the papillary muscles. In Nos. 238/I and 239 which died from the experimental procedure the hearts were much dilated and filled with coagulated blood, and in No. 239 gross hemorrhages were present throughout the endocardium of the left ventricle, the papillary muscles being particularly affected. Of the 2 dogs which died from intercurrent diseases, No. 388 showed marked dilatation of the heart with hemorrhages in the papillary muscles of the left ventricle, while No. 256 exhibited no more than acute parenchymatous degeneration.

The *microscopic examination of the hearts* showed 2 types of alterations, namely, (1) hemorrhages and necroses and (2) what appeared to be degenerative changes of individual muscle fibers. *Hemorrhage without necrosis* was observed in the 2 acute experiments which terminated fatally at the end of the experimental period (Nos. 238/I and 239). One of these dogs had been poisoned by inhalation, the COHb level exceeding 75% for 3 hours, and 80% for 80 minutes. If no necrosis developed, this was probably due to the fact that the animal expired before anatomic changes could manifest themselves. The other dog (No. 239) had been poisoned by transfusion, the COHb level exceeding 75% for 45 minutes and 84.4% for 10 minutes. But in this animal the blood volume had been increased 6.6 times, that is to

say, the amount of CO-free hemoglobin still equaled about 95% of the original quantity (see page 514). Whether or not necrosis would have developed here, if the animal had lived long enough, is question-

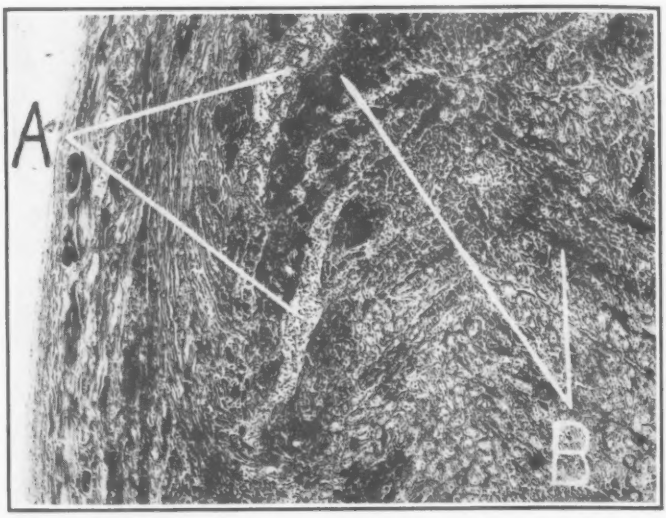

FIG. 2.—Dog 473. Killed 4 days after poisoning by inhalation. Note black areas of extensive subendocardial hemorrhage (*A*) and necrosis (*B*). (Mallory stain, × 92.)

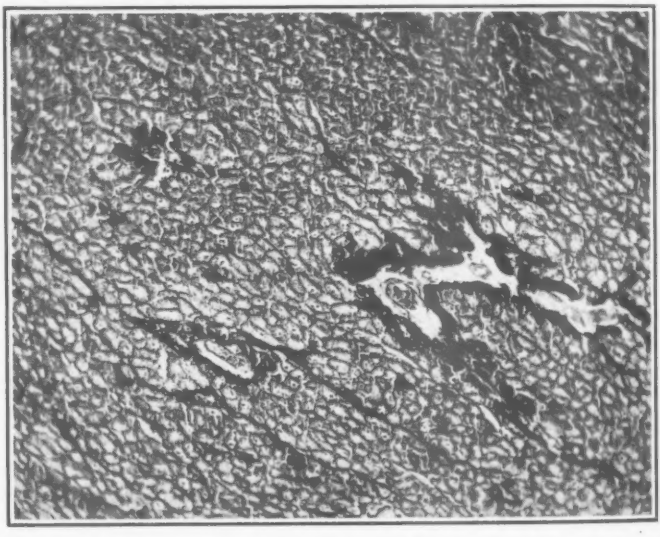

FIG. 3.—Same as Figure 2. Shows acute perivascular necrosis. (Mallory stain, × 149.)

able. It is conceivable that the hemorrhages in this dog were due solely to the enormous quantity of blood which was eventually in circulation.

Hemorrhages as well as necroses were present in CO No. 473 (Figs. 2 and 3) which was sacrificed, and in CO No. 388 (Fig. 4) which died from bronchopneumonia, both 4 days after an acute experiment. *Necroses alone* were found in Nos. 246 (Figs. 5 and 6) sacrificed 7 days after inhalation of CO, and Nos. 743 (Fig. 7) and 745 (Fig. 8) sacrificed 3 months after termination of chronic O_2 deficiency. Nos. 473, 388 and 246 were all poisoned by inhalation, their COHb level exceeding 75% for 1 hour or more. No. 473 was brought up to 76.7%, No. 388 to 82% and No. 246 to 90% COHb.

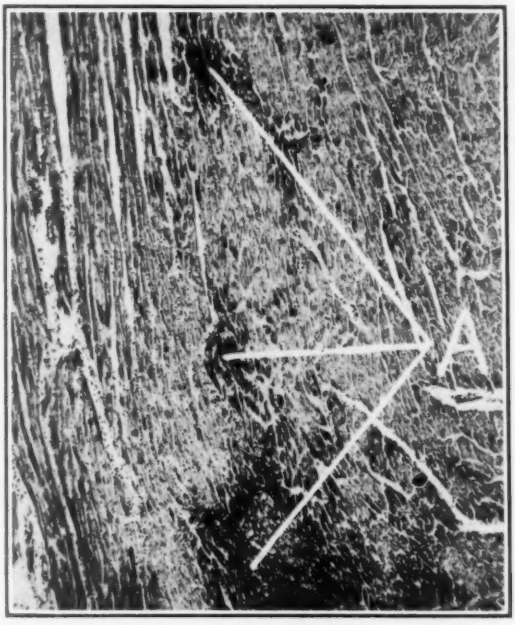

FIG. 4.—Dog 388. Died 4 days after poisoning by inhalation from confluent bronchopneumonia. Note dark areas of acute myocardial necrosis. (Hematoxylin-eosin, X 110.)

The hemorrhages and necroses were scattered especially through the subendocardial layers of the left ventricle with particular involvement of the papillary muscles (Figs. 2, 5 and 7). Fresh areas of necrosis were deep red in color when stained with hematoxylin-eosin, and purple or blue with Mallory's stain. In a good many places the necroses showed a definitely perivascular arrangement (Figs. 3 and 6). There were no leukocytes present at the time when the hearts were examined, but early organization was observed in No. 388, early calcification in Nos. 246 (Fig. 6) and 745 (Fig. 8) and late calcification in No. 743 (Fig. 7).

Of the 11 dogs which did not develop hemorrhages or necroses from acute poisoning, 7 never reached 75% COHb (Nos. 198, 233, 238/II, 249, 256, 324, 368). The other 4 reached levels from 75 to 84.3%,

but 3 of these remained above 75% for only 15 minutes or less (Nos. 258, 450, 615), while the fourth (No. 267) was kept above 75% for a little over 1 hour; but in this experiment the CO was given by transfusion and there was a marked increase in the number of erythrocytes

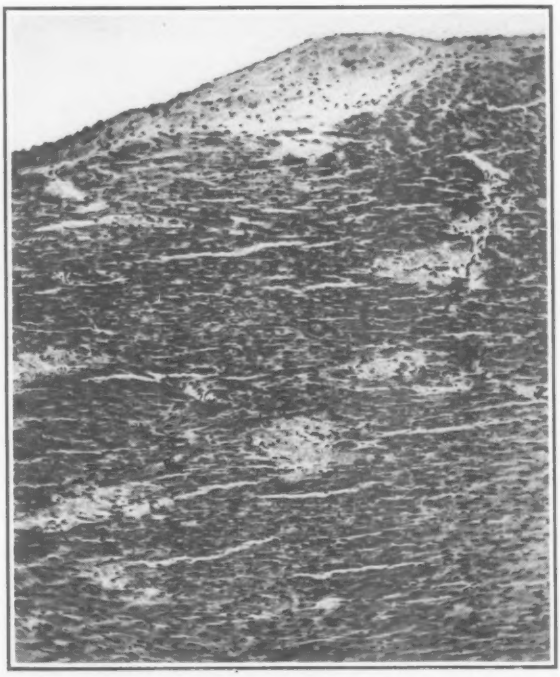

FIG. 5.—Dog 246. Killed 7 days after poisoning by inhalation. Shows extensive necrosis in papillary muscle. (Hematoxylin-eosin, × 135.)

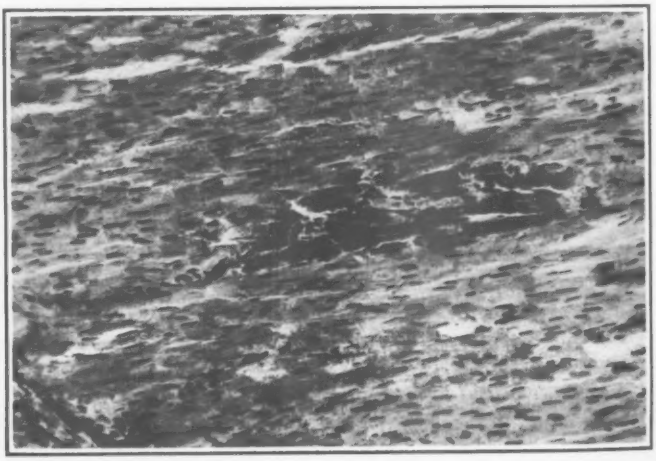

FIG. 6.—Same as Figure 5. Shows dark areas of early calcification of necrosis. (Hematoxylin-eosin, × 230.)

in the circulating blood so that the quantity of CO-free hemoglobin amounted to a greater percentage than that found in the animals which developed necroses.

In 1 of the 2 chronic O_2-deficient animals (No. 745), the necroses seemed to be fairly recent and were probably due to some pathologic

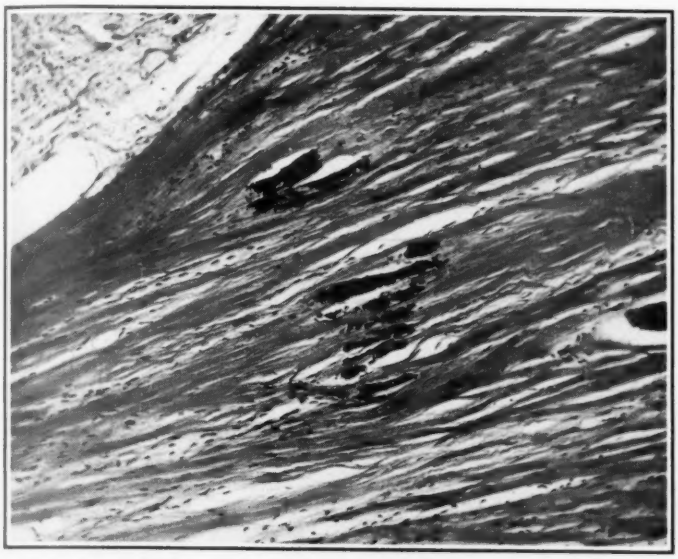

FIG. 7.—Dog 743. Killed about 4 months after period of chronic O_2 deficiency. Shows old calcified necrosis (black) of papillary muscle. (Hematoxylin-eosin, × 132.)

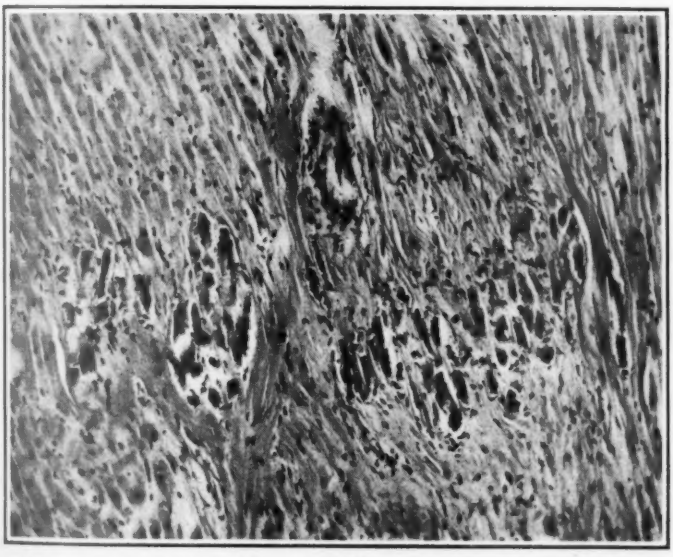

FIG. 8.—Dog 745. Killed about 4 months after period of chronic O_2 deficiency. Shows darker calcified necrosis of papillary muscle. (Hematoxylin-eosin, × 132.)

process during the course of observation; while they appeared old in the other (No. 743) and were possibly due to an episode preceding the experiment. The dog showing recent necroses had had a negative T wave while alive; the other had not been studied electrocardiographically.

The *degenerative changes of individual muscle fibers* which were mentioned above were found in one normal control dog (No. 266) (Fig. 9). Of the experimental animals, Nos. 233, 238/II, 256, 258, 324, 696 and 741 seemed to be free of these changes, and Nos. 198, 267, 368, 615 and 744 were questionably free; but No. 450 which was poisoned by inhalation up to 83.3% COHb was definitely positive, and there were marked degenerative changes (Fig. 10) in the chronic CO animals (Nos. 737, 739, 740, 749) and the chronic O_2-deficient animal No. 738.

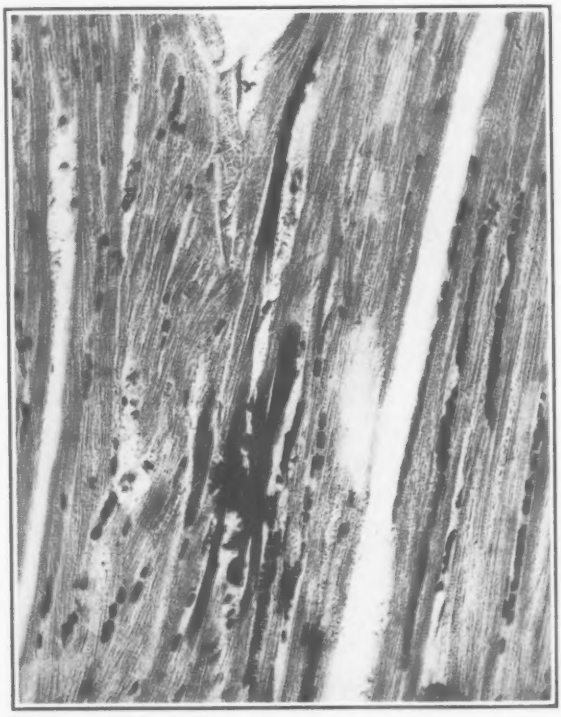

FIG. 9.—Dog 266. Control experiment. Longitudinal section. Altered muscle fibers staining bright orange appear black in photo. (Mallory stain, × 368.)

The microscopic appearance of these changes is best studied in Figure 9, representing a longitudinal section. It can be seen that the changed portions of the fibers were narrow and hyaline in appearance; they stained deep red with hematoxylin-eosin, and bright orange with an overdifferentiated Mallory stain; and they were often limited to segments between intercalated disks. The only changes reported in the literature resembling these alterations seem to be those which

Orsos[28] described as "vital reactions." However, whether our changes were "vital" or artefacts could not be decided, though it is noteworthy that 3 of these dogs had presented electrocardiographic changes while alive (Nos. 737, 738, 739); 1 had not been studied electrocardiographically (No. 749); and only 1 showed a normal electrocardiogram (No. 740).

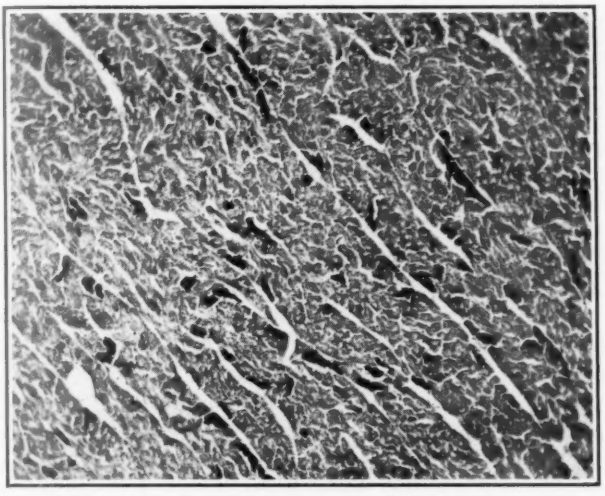

FIG. 10.—Dog 739. Cross-section of myocardium. Altered muscle fibers, staining bright orange appear black in photo. (Mallory stain, × 138.)

If we turn now to the *deposition of fat and hemosiderin* which are often found in circulatory disturbances, it may suffice to say that no significant differences in the fat contents were found in the various organs in the various experiments, though the renal tubules and glomeruli contained more fat in the chronic experiments than in the acute ones.

The amount of hemosiderin deposited in the spleen was found to be increased in the transfusion experiments, which seems to be explained satisfactorily by the introduction of so many erythrocytes into the circulation.

Discussion. Our findings in dogs closely resemble those obtained by previous investigators in experimental animals. Exposure to CO was followed first by decrease in amplitude of the T wave, inversion of the T wave, elevation of the R-T segment, and later by atrioventricular dissociation and A-V heart block. The changes in the T wave and R-T segment appeared in acute experiments at a COHb level of 40%, while heart block was observed only when the COHb level exceeded 75%. After a certain length of time, all animals maintained at this level collapsed, and there was evidence of respiratory failure and cerebral damage. These observations were confirmed in subsequent experiments which will be reported elsewhere.

In chronic experiments T-wave changes appeared after the 1st week of exposure to CO in 2 animals which manifested a COHb concentration of 21%.

Morphologic examination of the hearts revealed hemorrhages and necroses in the myocardium of all animals the COHb level of which exceeded 75% for 1 hour or longer; while those which remained beneath 75%, or exceeded this level for only 15 minutes or less, did not develop so severe alterations. Some of the latter, however, showed what appeared to be degenerative changes of individual muscle fibers. These were most prominent in our chronic CO experiments.

It thus appears that in dogs severe changes in the myocardium are produced only if the CO concentration exceeds 75% and is maintained at this level for not less than between 15 minutes and 1 hour; while moderate alterations were observed following chronic exposure leading to a COHb concentration of 21%.

It had been noted by previous observers that the electrocardiographic changes from CO poisoning closely resemble those observed in anoxia whether induced by O_2 deprivation,[9,14,18,22,23] pituitrin or adrenalin injection,[9] exertion,[4,9] anemia,[4] high altitude[29] or fear.[27] A similar resemblance was found to exist between the morphologic changes in CO poisoning and those produced by anemia, exertion, or low O_2 tension.[3,4,26] Klebs,[20] on the other hand, has pointed out that in man in CO poisoning, in contrast to asphyxia, no pleural hemorrhages were found; and Drinker[10] has noted that in CO poisoning nervous symptoms invariably occur before respiratory symptoms, while in asphyxia the latter preceded the former. Though these observations cannot be disregarded, it seems that they do not speak against an anoxic nature of CO poisoning, for here we deal with a slowly rising concentration of CO in the blood, resulting in a slow asphyxiation; while the cases of anoxia which Klebs and Drinker had in mind possibly were those of sudden catastrophe or violence resulting in almost instant death of the patient.

Summary. All experiments were performed upon dogs. Acute CO poisoning was produced in some animals by inhalation of the gas and in others by intravenous introduction of erythrocytes saturated with CO; while chronic poisoning was effected by exposure to 0.01 vol. % CO for $5\frac{3}{4}$ hours daily over a period of 11 weeks. As a control, chronic anoxia was produced in other animals by exposure to an atmosphere containing only 10 vol. % O_2.

The electrocardiographic changes observed were inversion of the T wave, elevation of the R-T segment, atrioventricular dissociation, and A-V heart block. The morphologic changes included certain degenerative changes of individual muscle fibers, as well as hemorrhages and necroses of the myocardium. While the changes in the T wave and R-T segment and the degenerative changes appeared as early as at 40% COHb in acute experiments, or at 21% COHb or an equivalent O_2 deficiency in chronic exposure, heart block and myocardial hemorrhages and necroses were observed only when the COHb level exceeded 75% for 1 hour or longer.

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It was noted that the electrocardiographic and morphologic changes of the heart in CO poisoning closely resemble those observed in anoxia due to other causes.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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ACUTE LARYNGOTRACHEOBRONCHITIS: A 25 YEAR REVIEW

BY MAJOR A. HARRY NEFFSON, M.C., A.U.S.

SIGNIFICANT literature concerning acute laryngotracheobronchitis first appears in the wake of the 1918 pandemic of influenza. Having been accustomed to regard cases of acute laryngeal obstruction as invariably due to diphtheria, the early writers were surprised to find that a number of patients with acute obstructive infections of the laryngotracheal airway did not follow the usual clinical course of a diphtheria patient treated with antitoxin and, moreover, showed no Klebs-Loeffler bacilli on culture. Thus, it seems that it required the impact of an epidemic of influenza, with its striking complications involving the respiratory tract, to awaken the medical profession to the need for a critical reëxamination and overhauling of their traditional ideas concerning so-called "croup." This was 25 years ago. Since then many changes have occurred in our conception of this disease.

It is the purpose of this review to trace these changes in our conception of the various aspects of the disease—namely, as regards the nomenclature, bacteriology, pathology, symptomatology, diagnosis, supportive and specific treatment, operative and postoperative therapy and the recognition and treatment of complications.

Historical. The first references calling attention to acute laryngeal obstruction caused by organisms other than the Klebs-Loeffler bacillus are scattered case reports. McNab[76] (1915) reported 1 case with membrane which on culture yielded only *Strep. hemolyticus;* Morris[79] (1917) reported 3 cases of laryngeal stenosis as a complication of measles—all 3 died; Gardner[39] (1918) reported 3 cases of necrotic and exudative inflammation of the larynx, trachea and bronchi caused by the *Staph. pyogenes aureus*—all died and showed pneumonia on postmortem examination. Lewis[63,64] (1918) reported 164 cases of membranous croup of which 61 were clinically diphtheria and 52 also bacteriologically diphtheria; in the rest (103 cases) only streptococcus was found. He said that cases of membranous croup are generally mistaken for diphtheria, whereas the streptococcus is the causative agent. He suggested the elimination of the term "croup" and "membranous croup" as misleading, and urged the use of the term "laryngitis." In the same year (1918) Gover[45] reported 96 cases of "membranous croup" of which 40 showed negative cultures for diph-

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theria; also 74 cases of "non-membranous croup" in which 54 showed cultures negative for diphtheria. He stated, "It has been felt that in the past many of the croup cases were not diphtheritic, but only a catarrhal laryngitis." Lynah[70] (1919) said, "During the recent pandemic of influenza I had an opportunity to study the laryngeal and tracheobronchial pictures in influenzal patients. Some were supposed to have diphtheritic laryngitis until laryngoscopy showed otherwise. During routine direct examination of croup cases in the Willard Parker Hospital they were surprised to find no membrane present." In 1921, Jackson[57] and Purcell[95] each reported a case of laryngeal stenosis not caused by the diphtheria bacillus. Thomson[108] (1922) reported that out of 810 patients admitted to the Willard Parker Hospital with a diagnosis of laryngeal diphtheria, 113 had "acute stenotic laryngitis" due to measles, scarlet fever, influenza, and other infections. In 1924, Smith[103] reported 4 cases in which only *Strep. hemolyticus* was found and Lynch[71] reported 5 patients tracheotomized because of laryngeal obstruction, in all of whom only *Staph. albus* was cultured. In the same year Baum[2] reported 4 patients with laryngeal obstruction requiring tracheotomy in whom the causative agent was *Strep. hemolyticus;* he designated this condition as acute laryngotracheobronchitis, which presumably is the first reference to this term in the literature. In 1925 Dixon[32] reported 1 case due to streptococcus and staphylococcus, and Strachan[106] reported 3 cases due to *Strep. hemolyticus,* staphylococcus and *B. influenzæ* with fatal results. In the same year (1925) Lewis[66,67] reported 4 deaths from membranous laryngotracheobronchitis complicating scarlet fever and caused by streptococcus. In 1926 Daily[27] reported 1 case and Allen and Husik[54] reported 2 cases of laryngeal obstruction requiring tracheotomy, in which the diphtheria bacillus was absent. Gittins[41] (1926) reported 14 cases of non-diphtheritic laryngeal obstruction, mostly due to streptococcus. In 1932 he said, "The Klebs-Loeffler bacillus is blamed for many conditions it doesn't cause. In 1920 we realized for the first time that there are non-diphtheritic infections of the larynx, trachea and bronchi in which the onset and symptoms simulated diphtheria, but in which antitoxin gave no relief and the mechanical obstruction below the cannula was decidedly more troublesome than in diphtheria." Tucker[111] and Hart[50] (1927) each reported a case due to a non-diphtheritic infection, that of the former requiring tracheotomy. In 1928 Baum[3] reported 24 cases of acute laryngotracheobronchitis in children. In his discussion of Baum's paper, Forbes[37] asks, "Is acute laryngotracheobronchitis a comparatively new picture? Was it common before the great influenza pandemic 10 years ago? Why doesn't this serious complication of our seasonal epidemic respiratory infection receive more attention in our recent textbooks? (This question is still a valid one today.—Ed.) Fifteen years ago we were taught in medical schools that laryngeal diphtheria is about the only disease requiring intubation. . . . . In Denver in 8 years I have not treated 1 case of laryngeal diphtheria, but I've seen 15 cases of acute laryngotracheobronchitis requiring surgical intervention."

With this report by Baum,[3] in 1928, may be said to have come to an end the early phase of the conception of this disease. Since that time notable contributions to the various aspects of this subject have been made by Arden and Duhig,[1] Baum,[2–10] Brennemann *et al.*,[15] Davison,[29,30] Galloway,[38] Gilbert *et al.*,[40] Gittins,[41–44] Holinger,[52,53] MacCready,[72,73] Michels,[77,78] Neffson and Wishik,[81–89] Orton *et al.*,[91] Richards,[96,97] Sinclair,[101] Tolle[110] and others. These will be noted under the proper headings.

Nomenclature. Since Baum's suggestion in 1924, the term "acute laryngotracheobronchitis" has been coming into general acceptance as a designation for this condition. That this name is not completely satisfactory, however, is apparent from the statements of several writers.

Richards[96] (1933) stated, "We have been able to formulate a definite disease entity from a clinical and pathologic study of 11 cases recently encountered . . . . fulminating laryngotracheobronchitis."

Neffson and Wishik[81] (1934) defined the term "croup" as the symptom-complex due to any stenosis of the laryngotracheal air passages and proposed the term "acute infectious croup" to include all those cases of respiratory tract obstruction that were due to infection. Further, to those obstructions not caused by diphtheria, they gave the general designation "acute non-specific infectious croup" which included acute laryngitis, acute laryngotracheitis and acute laryngotracheobronchitis. Moreover, they urged that in describing each particular case, both the etiology and the extent of involvement be given whenever possible, *e. g.*, acute streptococcic laryngitis, acute staphylococcic laryngotracheitis and acute pneumococcic laryngotracheobronchitis. They warned of the tendency of certain workers to include relatively mild cases of laryngitis and laryngotracheitis in the more serious group of acute laryngotracheobronchitis, "which is characterized by extreme subglottic swelling associated with profuse secretions poured out from the entire extent of the tracheobronchial tree;" and they pointed to the . . . . "value of an anatomic grouping from the standpoint of therapy, prognosis and as a basis for comparing results of different workers." They also differentiated these cases when they occurred as complications of the exanthemata.

Brennemann *et al.*[15] (1938) stated, "A sharp differentiation according to the precise nature of the involvement in a given case is not always a simple matter, especially as one must find its exact place in a series of manifestations that range in severity all the way from simple catarrhal laryngitis to rapidly fatal fulminating laryngotracheobronchitis." Brighton[16] (1940) wrote, "Only cases requiring tracheotomy should be considered as acute laryngotracheobronchitis." Orton *et al.*[91] (1941), however, included cases in which surgical procedure was not needed. They said, "Every child with acute laryngitis is potentially a victim of acute laryngotracheobronchitis until proven otherwise. . . . . In the early cases it is hard to differentiate them; after improvement it is also hard to tell them apart. Beginning as acute laryngitis, it may stay that way or go on to acute laryngotracheitis or acute laryngotracheobronchitis."

Gilbert *et al.*[40] (1941) stated, "Failure to standardize the nomenclature constitutes a challenge to those responsible for the care of patients with this disease. This challenge may be considered answered only after a proper classification of croup has been accepted. . . . . A practical classification should automatically yield a clue to the appropriate management as well as to the immediate prognosis in each case of croup. . . . . The term 'croup' designates a state of obstruction to the entrance of the air into the lungs as a result of an inflammatory process in the larynx or extending to the lower respiratory tract. There are two main types, diphtheritic and nondiphtheritic. . . . . The term 'acute obstructive laryngotracheobronchitis' is used in preference to 'acute laryngotracheobronchitis' or 'acute fulminating laryngotracheobronchitis,' because the element of obstruction is the predominant feature. . . . . 'Acute hemorrhagic necrosing tracheobronchitis,' associated with 'acute hemorrhagic pneumonitis' (so-called 'inflammatory pneumonitis'), but without subglottic edema should

not be included. Pneumonia with associated mild catarrhal inflammation of the laryngotracheobronchial tree is excluded. . . . . Recently obstructive laryngotracheobronchitis has enjoyed prominence in the literature to the exclusion of most other varieties of croup. Careful analysis of the related pathologic conditions, symptoms and clinical data reported leaves considerable doubt as to the accuracy of diagnosis in some cases. . . . . At present all types are placed in the group of acute laryngotracheobronchitis regardless of whether they have bronchial or pneumonic involvement or not." They present a "comprehensive classification" as follows: "Non-diphtheritic croup": (*a*) acute catarrhal laryngotracheitis, (*b*) supraglottic edematous obstructive laryngitis, (*c*) subglottic obstructive laryngotracheitis—(1) edematous type and (2) exudative or inspissated type—and (*d*) acute obstructive laryngotracheobronchitis.

Gittins[44] (1942) uses the term "infectious laryngotracheobronchitis" and calls the condition a symptom-complex. He classifies laryngotracheobronchitis into four types: infectious, traumatic, allergic and spasmodic. The infectious type he subdivides into "(*a*) nonspecific (streptococcus, staphylococcus, influenzal, pneumococcus, etc.) and (*b*) specific (diphtheria)."

MacCready[73] (1944) wrote, "In view of the pathology it seems unwise to refer to any of these cases, even the milder ones, as laryngitis alone. . . . . The only patients in this series which fall into this group (laryngitis) died from profound inflammation of the glottis, before it had time to extend to the trachea and bronchi." (This seems to be a rather dangerous assumption, because cases of acute edematous obstructive laryngitis are often self-limited.—ED.)

Baum[10] (1944) said, "It (acute laryngotracheobronchitis) is not a specific clinical entity, but a symptom-complex. . . . . There is a primary infection with the virus of influenza and a secondary invasion by the streptococcus. . . . . It is a symptom-complex of different degrees of severity." Holinger,[53] discussing Baum's paper, asked, "When is it acute laryngitis and when acute laryngotracheobronchitis?" He said that pulmonary findings are an essential factor in the diagnosis and also stressed the disease as a symptom-complex.

Thus, it is evident that there is still need for agreement on an all-inclusive, general term denoting acute non-diphtheritic infectious obstruction of the laryngotracheobronchial airway, with (*a*) specific anatomic subdivisions indicating the extent of involvement and (*b*) possibly also pathologic descriptions of the cause of the obstruction. Acute laryngotracheobronchitis is only one phase of the whole picture; if used correctly the term describes the most severe and dangerous affection found in this condition. However, its frequent and casual application to cases with mild, moderate or even severe involvement of the larynx and trachea only, has led to much confusion when comparing types of therapy, prognosis and results of different workers.

That this disease is not a clinical entity, but rather a symptom-complex is gradually becoming apparent.

Bacteriology. Many organisms have been implicated as the agents in this disease. Not only have they varied in different localities, but also at different periods in the same locality. Since many of these cases occurred during epidemics of influenza, which at one time was thought to be caused by the *B. influenzæ*, it was only natural for many to believe that this organism was the prime factor. However, since recent work has shown influenza to be caused by a virus, opinion has been veering to the view

that the various organisms recovered in this disease are merely secondary invaders in a soil made fertile by the virus of influenza. Some confusion has resulted from the fact that some writers still think of the *B. influenzæ* as the etiologic agent in true influenza.

Chronologic reports of the bacteriology in this disease follow: McNab[76] (1915) 1 case—streptococcus; Gardner[39] (1918) 3 cases—*Staph. aureus;* Lewis[64] (1918) stated that streptococcus is the most common organism found; Smith[103] (1924) 4 cases—*Strep. hemolyticus;* Lynch[71] (1924) 5 cases—*Staph. albus;* Lewis[66] (1925) 4 deaths in scarlet fever with laryngeal obstruction—*Strep. hemolyticus;* Dixon[32] (1925) 1 case—streptococcus and staphylococcus; Strachan[106] (1925) 3 cases—all died—*Strep. hemolyticus,* staphylococcus and *B. influenzæ;* Gittins[41] (1926) 14 cases—streptococcus predominating, with staphylococcus and pneumococcus less frequently, *B. influenzæ* occasionally; Hart[50] (1927) 1 case—*Strep. non-hemolyticus;* Leigh[62] (1927) 4 cases—staphylococcus, pneumococcus and streptococcus; Berry[13] (1928) 1 case—died—*Staph. aureus hemolyticus.* In 1930 Cultra and Streit[26] reported 13 cases in which the predominating organism was the staphylococcus; Bradford and Leahy[14] reporting 28 cases found mostly *Strep. viridans,* only 5% *Strep. hemolyticus.* From Australia in the same year (1930), King[61] reported 1 case in which no Klebs-Loeffler bacilli were found; Mathew[75] reported 4 cases with *Staph. aureus;* Beare[11] reported 10 cases—8 *Staph. aureus* and 2 pneumococcus. Richards[96] (1933) found *Strep. hemolyticus* in pure culture in all cases that came to postmortem examination; staphylococcus and pneumococcus were occasional secondary invaders. Neffson and Wishik[82] (1934) reported the bacteriology in 254 cases as follows: Pure cultures—*Strep. hemolyticus* in 72 cases, *Strep. viridans* in 45 cases, *Staph. aureus* in 13 cases, *B. influenzæ* in 3 cases; some type of streptococcus, alone or combined with other organisms, was found in 234 cases (92%); *Strep. hemolyticus,* alone or in combination, in 177 cases; *Strep. viridans,* alone or in combination, in 130 cases; *Staph. aureus,* alone or in combination in 71 cases; *B. influenzæ,* alone or in combination, in 10 cases. Smith[104] (1936) reported 43 cases with *Strep. hemolyticus* in 26, *Strep. viridans* in 23, *Staph. aureus* in 17, pneumococcus in 5; in 4 fatal cases *Strep. hemolyticus* and *Staph. aureus* were recovered. Jackson[58] (1936) stated that the streptococcus was found in over 90% of the cases, the *B. influenzæ* in 5%. From Puerto Rico, Font and Ortiz[36] (1939) reported 6 cases due to the *Staph. aureus hemolyticus*—3 died; they stated that there was no apparent difference between these cases and the ones caused by the *Strep. hemolyticus.* Neffson and Bullowa[85] (1938) reported a case of acute laryngotracheobronchitis with septicemia, meningitis and endocarditis due to *B. influenzæ.* Sinclair[101] (1941) reported 10 cases of laryngitis with septicemia due to *H. influenzæ* type B. In these cases severe prostration accompanied the laryngeal obstruction. He quoted Pittman[93] who found that the pathogenic strains of *B. influenzæ* are usually encapsulated and the capsules have a specific soluble antigen which renders them capable of differentiation into the serologic types A to F. The majority of strains isolated from influenzal meningitis are type B. Sinclair showed that the septicemias with laryngitis were due to type B. De Navasquez[31] (1942) also cited a case of laryngitis with septicemia due to *H. influenzæ* type B. Orton *et al.*[91] (1941) reporting 45 cases found streptococcus in 11, streptococcus and staphylococcus in 13, streptococcus and pneumococcus in 10, staphylococcus in 4, pneumococcus in 2, streptococcus, staphylococcus and pneumococcus in 4, staphylococcus and pneumococcus in 1. Neffson[88] (1942) tracing the incidence of bacterial infections

in 126 tracheotomized cases during 1931–1940, found that there was a remarkable increase in the frequency of *Staph. aureus* infections since 1938; in fact there were twice as many infections with the *Staph. aureus* as with the *Strep. hemolyticus* during the period 1938–1940. On the other hand, during the period 1931–1934 there were 5 times as many infections caused by the *Strep. hemolyticus* as due to the *Staph. aureus*. Walsh[113] (1944), reporting 101 cases, found the predominating organism to be a staphylococcus combined with streptococcus and pneumococcus; also some *B. influenzæ* and 1 *B. friedlander*. MacCready[73] (1944) reported that 3 cases due to *B. influenzæ* were treated in 1931 and 4 cases with septicemia due to *H. influenzæ* type B were seen in 1941–1942; he states that there were none in 1943, but there were many with pneumococcus type 6. Arden and Duhig[1] (1944) report 5 cases in which *Staph. aureus* was recovered; there were 3 deaths; in 2 of these there was a necrotic laryngotracheobronchitis, in the other severe supraglottic edema.

Discussing a paper by Gittins in 1936, Baum[7] expressed the view that the basic cause of acute laryngotracheobronchitis was the filtrable virus of influenza.

Brighton[16] (1940) called attention to an almost identical disease of chickens—infectious laryngotracheitis—as shown by Beech[12] in 1931. He suggested that acute laryngotracheobronchitis in humans is the result of a virus infection with secondary invasions of the various bacteria which we have found. (Beech stated that there was in use a successful virus vaccine against this disease in chickens.)

Neffson[86] (1940) stated that there was a strong possibility that the recent epidemic may have been caused by a virus infection with secondary invaders, because (*a*) the laryngologic picture, with the more than usual amount of supraglottic edema and the tendency to ulceration, was similar to that found in measles, (*b*) the organism recovered was the same—*Staph. aureus*, and (*c*) the W.B.C. count was depressed just as in virus infections.

MacCready[72] (1940) stated that acute laryngotracheobronchitis occurs sporadically during influenza and measles epidemics; furthermore, he said, "It used to be thought that the streptococcus was a factor, but now it is felt to be an influenzal type of infection with secondary invaders."

Orton *et al.*[91] (1941) stated that they found no proof of virus infection, but the low blood count in some cases suggested virus disease.

MacCready[73] (1944) asserted, "While the virus may initiate the process, the symptoms produced by the bacterial or secondary infection may not necessarily occur concomitantly. They may not appear for 1 or 2 weeks. This directs most of the attention to the bacteria as the etiologic agent which it is necessary to combat in this disease. When pneumococci are present as the pathogens the picture is apt to be not as severe as with other pathogens . . . . the *Staph. aureus* is . . . . only a contaminant." He states that the *H. influenzæ* type B causes the most serious symptoms and he suggests that it may bear a closer etiologic relationship to this disease than any of the other pathogens commonly found.

Arden and Duhig[1] (1944) reasoned that the fact that so many organisms have been incriminated and the similarity of this disease to that of laryngotracheitis in virus infections of chick embryos shows the close identity between the two diseases. From histologic studies (to be described later under Pathology) and comparisons with infectious laryngotracheitis and influenzal virus infections in chick embryos, as shown by Burnet and Folley,[18] they conclude that, ". . . . we believe that we are dealing with a disease

which has a specific and uniform pathology, which cannot be accounted for by any bacterial infection, but which . . . . is due to a virus . . . . (which) . . . . is not an influenza virus . . . . though there may be some relation between the two viruses."

Pathologic Anatomy. Winternitz *et al.*[116] (1920), describing the pathology of influenza, stated that the mucosa of the trachea and bronchi is very red, covered with exudate and shows superficial ulceration, which does not result in scarring. The bronchioles are full of exudate and pus and ulcerations here often extend to the submucosa and the muscular layer; the ulceration may be local or the entire circumference of the tube may be involved. The inflammation occasionally extends down to the duct of the mucus gland, which is involved in an aplastic inflammatory reaction. In the early stages there is an outstanding absence of polymorphonuclear leukocytes.

Cultra and Streit[26] (1930), reporting 13 cases, described exudation of a thick sticky mucus and swelling of the larynx. The mucosa was congested and beefy red in appearance. They said that the dyspnea and cyanosis are caused by bronchospasm and the gluing together of the lumen. Beare[11] (1930) described 5 cases that came to postmortem examinations; there was intense inflammation of the larynx and trachea and a patchy atelectasis and emphysema of the lung.

The first comprehensive description of the pathology of acute laryngotracheobronchitis was given by Richards[96] in 1933. He stated that the changes were essentially those of an acute descending inflammation of the upper respiratory tract with the extent of the involvement depending upon the duration of life after onset of symptoms. He described (1) a diffuse acute cellular infiltration and destruction of the walls of the larynx, trachea and bronchi—the histologic picture being comparable to that of a cellulitis of the skin; (2) a second type of lesion was seen in the destruction of the mucosa and the masking of the mucosal surfaces by fibrin and purulent exudate; (3) in those cases where a superimposed infection with staphylococcus occurred, a more marked destruction of the mucosa and wall of the trachea was noted as a manifestation of the necrotizing characteristics of that organism; (4) in the lungs there was peribronchial reaction and polymorphonuclear infiltration of the alveolar walls. He mentions a case in which a child died suddenly 54 days after the original infection. Postmortem examination showed that the mucosa of the trachea had been repaired and replaced by stratified squamous epithelium; there was slight peribronchial infiltration and some mediastinal emphysema.

Neffson and Wishik[82] (1934) described the "living pathology" as consisting of edema, exudation, membrane formation and spasm. The edema and congestion may be limited to the supraglottic or the subglottic structures, or may involve both and extend down to the bronchi. The exudation varies in amount and character. In mild cases it is scant or absent; in severe cases, with involvement of the trachea, bronchi and bronchioles, exudation is always profuse, usually thick and tenacious, and sometimes so ropy that it cannot be expectorated. If it is not removed it becomes gummy, often hindering the separation of the vocal cords and plugging the subglottic regions. In this region it can become dry and hard and resemble a foreign body. Membrane is found in severe infections, but this is usually thin. In more virulent infections, thick membrane, indistinguishable grossly from diphtheritic membrane was removed from the larynx, trachea and bronchi. Postmortem examinations in 12 out of the 19 fatalities in their series of 400 cases showed pneumonia, atelectasis, emphysema,

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empyema, mediastinitis, myocarditis and various other lesions secondary to septicemia. They also described the morbid anatomy in measles with laryngitis based on necropsies on 5 patients. In 4 cases there were extensive ulcerations of the larynx and trachea with exposure and erosion of the laryngeal cartilages and tracheal rings; pseudomembrane covered 2 of these ulcerated areas. Extensive bronchopneumonia was present in all 5 cases. It was also noted that in these patients there was a greater degree of supraglottic edema than in the usual run of non-specific cases.

Jackson and Jackson[58] (1936) described redness, swelling, secretion, the drowning of the patient in his own secretions, and crust formation. Richards[97] (1938), commenting on the low incidence of obstructing crusts, said this ". . . . may have been due to more zealous attempts to provide adequate moisture in the inspired air or to the use of solvents instilled directly into the trachea . . . . associated with a lowered virulence of the infection and a fortunate absence of a secondary invasion by the staphylococcus." Clerf[23] (1939) stated that "The greatest pathologic finding is the marked subglottic swelling."

Brennemann *et al.*[15] (1938), in an excellent description, stated, "The first signs of obstruction are usually due to the marked inflammatory swelling and edema of the loose subglottic tissue. If infection spreads, the same series of changes occurs in the trachea and bronchi except that with a less loose submucous tissue there is less swelling. The irritation of the infection is presumably the cause of the increased secretion of the tracheobronchial glands, the secretion being at first serous and later mucous. As the infection continues, not only are edema and acute inflammatory cells present in the submucous tissues, but other changes occur, such as extravasation of fibrin, fibrinoid degeneration of the connective tissue and lymphatic and capillary thrombosis. Simultaneously, the infection may cause necrosis of the epithelium, and exudate, fibrinous or fibrinopurulent, may be discharged onto the surface and become intimately mixed with the mucus which is being secreted. . . . . It is apparently the mixture of mucus, fibrin, polymorphonuclear leukocytes and degenerated epithelial cells which make the typical gummy, ropelike exudate and the crusts. The mucous glands and excretory ducts seem to offer moderate resistance to the infection and hence do not appear to be altered anatomically early in the disease. As the disease progresses to its later and more severe stages, however, sufficient damage may be done to these glands themselves to cause various degrees of degeneration and necrosis. When sufficient glandular damage has occurred, no further mucus is secreted, and gray fibrinous or fibrinopurulent exudate is discharged on the necrotic surface, producing the dry, glazed appearance noted grossly at bronchoscopy and at autopsy. . . . . Apparently this sustained glandular integrity and function, as judged from the bronchoscopic picture and the presence of relatively little anatomic glandular change, as compared with that of the surrounding tissue, until noticeably late in the disease, are somewhat different from the changes which occur in diphtheria, in which, according to Councilman, Mallory and Pearce,[25] the glandular necrosis is almost specific and may take place with little damage to the surrounding tissue. The principal difference, however, is in function, with undoubted stimulation in tracheobronchitis and suppression in diphtheria, the suppression being possibly due to the action of the soluble toxin in diphtheria. . . . . The ropelike secretions and the dried crusts cause partial or complete obstruction to the bronchi and to the bronchioles, with resulting atelectasis and compensatory emphysema or obstructive emphy-

sema, the type depending on the degree of occlusion. Spontaneous pneumothorax may occur from rupture of an emphysematous bleb. Pulmonary edema, interstitial pneumonia, lobular pneumonia and septicemia are common complications in fatal cases."

MacCready[72] (1940) stated, "Histologically the mucosa is destroyed over large areas and replaced by fibrin, mucus and red cells. The submucosa is edematous and congested. Similar changes occur in the smaller bronchioles. When *B. influenzæ* was recovered the pathologic picture was less marked than with streptococcus; with the staphylococcus, necrosis is more pronounced."

Grier[49] (1941) described a characteristic mediastinal enlargement in acute laryngotracheobronchitis. The enlargement was found in the superior mediastinal shadow. It was symmetric and projected on both sides of the spine, the edges usually being concave, but occasionally straight. He differentiated this from the thymus shadow which is almost always a bulging shadow with convex borders.

Orton *et al.*[91] (1941) reported their findings in 8 postmortem examinations as follows: Crusts and mucopus were found in the nose; the pharynx and tonsils were inflamed; the mucosa of the larynx, trachea and bronchi were red and swollen, with thick, somewhat adherent, mucopurulent exudate which separated easily from the underlying tract and left no gross area of erosion. The smaller bronchioles were red and contained glairy, bloody material. The glands at the hilus of the lungs and along the trachea and bronchi were enlarged and congested. The lungs showed patchy consolidation and the bronchioles contained tenacious mucopus. On microscopy the smaller bronchi were found filled with pus and the walls infiltrated with polymorphonuclear leukocytes. The lining epithelium was degenerated or missing in places. The alveoli surrounding these bronchi were distended with purulent exudate. The walls were swollen, the lining ulcerated, and the alveoli partly collapsed. There were areas of atelectasis, emphysema and bronchopneumonia. They stated that in streptococcic infections there is fiery redness and swelling of the subglottic and tracheal regions, while the true cords may show very little reaction. Later, necrotic and gangrenous pseudomembranes may be seen extending down to the tracheal bifurcation and into the main bronchi. First it is the subglottic edema. Later the membrane which causes the obstruction. In staphylococcic infections the inflammation is accompanied by the formation of dirty gray, thick, tenacious plugs which tend to dry and crust and rapidly cause marked progressive obstructive symptoms. Six of their 62 patients had a pseudomembrane in the larynx. Removal of these crusts leaves no mucosal necrosis, which occurs later in streptococcic infections.

Gilbert *et al.*[40] (1941) found that, in the subglottic exudative or inspissated type, the vocal cords are immobile, being separated by exudate or crusts with relief on removal of these obstructions. In the edematous type, the obstruction is due to edema and the interference with motion of the cords, preventing complete abduction. In acute obstructive laryngotracheobronchitis the tracheal lumen is so narrowed at times as to make the passage of the bronchoscope difficult or impossible. Patients with subglottic edematous obstructive laryngotracheitis can enjoy relief and progress favorably for several days after tracheotomy; then the airways will become obstructed with thick exudate. . . . . Inasmuch as the transition is incident to the secondary infection, cases in which this occurred are not included in acute obstructive laryngotracheobronchitis. They state

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that in supraglottic edema the lingual surface of the epiglottis is more involved than the laryngeal surface. They believe this type to be self-limited. (I concur in this observation, contrary to the opinion of some, *e.g.*, MacCready.—Ed.)

Neffson[88] (1942) presented sections of the larynx, trachea and bronchi demonstrating the following: metaplasia and ulceration of the epithelium and infiltration of the submucosa, mucous glands and muscles with plasma cells; necrosis of the epithelium and membrane formation; diffuse cellular infiltration of the tracheal bifurcation with monocytes and polymorphonuclear leukocytes and fibrinopurulent exudate replacing the epithelium and the necrotic duct of a mucous gland. In a case of measles with ulcerative laryngotracheobronchitis there was seen diffuse infiltration of the larynx, trachea and bronchi with plasma cells, denudation of the epithelium, infiltration and destruction of the mucous glands with desquamation of the glandular epithelium. In a case of scarlatinal laryngotracheobronchitis the larynx showed denudation of the epithelium, generalized edema, and diffuse polymorphonuclear infiltration extending down to the perichondrium, together with abscess formation. In a case of varicella with acute obstructive laryngotracheobronchitis, the larynx showed infiltration, necrosis and denudation of the epithelium, monocytic infiltration between muscle bundles, deposition of fibrin and purulent phlebitis; the trachea showed the same picture including desquamation of the glandular epithelium. He stated that there is often dense infiltration of the subglottic tissues, the formation of occasional strictures and webs (not due to intubation), and the occurrence of prevertebral edema with compression of the trachea, which are factors in delayed decannulation following tracheotomy. He also noted enlargement of the superior mediastinal shadow in roentgenograms of patients with acute laryngeal obstruction, as described by Grier. He describes several cases in which secretions accumulated in the trachea and bronchi in from 1 to 4 days following decannulation. In these cases aspiration of the airway was necessary. In 1 child 6 months old, the tube was removed and the wound closed 2 months after operation. The next day respiratory distress developed and was relieved by suction of the trachea and bronchi. This was done 3 times, the third time without relief. Postmortem examination showed thick mucopus in the trachea and bronchi, which caused asphyxiation. There was no tracheal stenosis. (Possibly the observation of Hilding that ciliary destruction occurs in these cases could explain the accumulation of the mucopus.—Ed.)

Hilding[51] (1943) described a case of acute laryngotracheobronchitis in an adult. At necropsy the entire bronchial tree was found to contain thick, tenacious plugs of mucus. Microscopic examination revealed that the entire bronchial and bronchiolar epithelium had been sloughed off down to the last layer of stellate cells next to the basement membrane; there was not a vestige of a cilium anywhere. The lumens were filled with purulent exudate. He stated, "This patient would probably not have died of asphyxia had the ciliary mechanism been there to remove the thick secretion. Conceivably, aspirations through a tracheotomy might have saved him."

Baum[8] (1943) stated that the outstanding lesions are mucosal and submucosal inflammatory edema, most marked in the looser connective tissue of the subglottic region, but extending down to the trachea and bronchi. Later there are exudation and destructive lesions. Laryngotracheobronchitis causes serious alterations in the function of the tracheobronchial

glands and in the character of their secretions. He asserted that these changes make the glands and the secretions more susceptible to adverse influences such as the drying effect of the direct blast of even warmed and moistened air through the tracheal cannula. He said that no one has reported primary plugging of the bronchi with crusts, without tracheotomy.

Walsh[113] (1944) found (1) destruction of the epithelium and cilia, (2) tenacious thick pus and mucus which in severe cases seemed to be fixed to the goblet cells of the remaining epithelium and (3) marked edema of the tracheal and bronchial tissues. He said that bronchoscopy did not always give relief, showing that laryngeal edema is not the primary factor. On the other hand, bronchoscopic suction with removal of the thick secretions did give relief.

Arden and Duhig[1] (1944) described widespread necrosis of the mucosa unaccompanied by any cellular exudate. When the crust and exudate were removed, the underlying trachea was seen to be a dirty, brownish purple color, completely lacking luster, and quite different from the bright, purplish red commonly found in influenzal infections. The exudate extended to the main bronchi. Histologically there was complete destruction of the mucosa, with no cellular exudate, only débris, and submucosal vascular dilatation with some lymphocytic infiltration. They remark that this is unlike a bacillary infection, but resembles a virus infection. They found complete integrity of the mucus-secreting glands and their ducts (unlike that seen in diphtheria). Also, they did not find the typical lung involvement as in an influenzal virus infection; therefore, they reasoned that this was not of influenzal virus origin, though there is a relationship between the two viruses.

Incidence. *Frequency.* Orton et al.[91] (1941) state that, "In all over 300 cases have been reported since 1918." They apparently overlooked the report in 1934 by Neffson and Wishik[82] of 400 consecutive cases admitted between 1931 and 1934 to the Willard Parker Hospital because of non-diphtheritic laryngeal obstruction. This makes over 700 cases, not counting the number that have occurred without ever having been reported.

Seasonal. In the above-mentioned report by Neffson and Wishik, the disease was found to be "endemic the year round with a low ebb in June, July and August." However, Baum[9] (1943) and others state that the disease is seasonal and more severe during influenza epidemics. It is quite possible that the difference in conclusions arises from the fact that diseases of different etiology, but similar symptomatology, are involved.

Age. Berry[13] (1928) reported a case in an adult with crusting and suppuration of the entire respiratory tract, in which a pure culture of *Staph. aureus hemolyticus* was recovered; Davis[28] (1936) likewise reported a case in an adult. Michels[78] (1942) reported a case in an infant 5 weeks old. Neffson and Wishik,[82] in their series of 400 cases, found the age to range from 3 months to 50 years; 11.7% were under 1 year; 46% were 1 and 2 years old; 78% were under 5 years of age; 16.5% from 5 to 9 years; 5.5% were over 9; 11 patients were over 16 years of age.

Sex. It is generally agreed that this condition occurs more often in males than females. Specifically, the report of Neffson and Wishik[82] showed that there were 72% males as compared to 28% females. Neffson[88] (1942), reporting a series of 126 cases tracheotomized for non-diphtheritic laryngeal obstruction, found that 70% were males and 30% females. This shows that males are affected almost $2\frac{1}{2}$ times as often as females. Why this should be so, since the large majority of cases occur under 5 years of age, is a matter of conjecture at the present time.

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Symptomatology. A general description of the symptomatology is given by almost every writer on this subject. Briefly, there are hoarseness, cough, signs of respiratory obstruction and the usual reactions to infection, namely fever, leukocytosis and evidence of toxemia—with much variation both in the rapidity of onset and the degree of severity. Because of the lack of unanimity as to what constitutes acute laryngotracheobronchitis, descriptions of the symptomatology are quite varied. Thus, some describe respiratory obstruction of moderate degree and little or no signs of toxemia, whereas others picture patients suffering from extreme respiratory obstruction and toxemia of overwhelming proportions. In some cases the respiratory obstruction required operative intervention such as intubation or tracheotomy, while in others palliative measures alone were sufficient.

For the purposes of this review it is felt that only those observations describing unusual or characteristic signs and symptoms of value in diagnosis need be noted.

Mainzer[74] (1929) stated, "Infections of this type may easily be mistaken for laryngeal diphtheria, but in these (latter) cases the voice is usually lost." Neffson and Wishik[82] (1934) pointed out that cough occurred first, followed by dyspnea and later by hoarseness. They noted that this was different from diphtheria in which there is cough, followed by hoarseness and later dyspnea. They explained this difference on the basis of the underlying pathology, namely that in diphtheria membrane forming on the vocal cords, first prevents them from vibrating and approximating normally, causing hoarseness. Later, when enough membrane has formed dyspnea appears. On the other hand, in the non-diphtheritic case, edema is usually produced above and below the vocal cords and often the cords themselves are not involved, because the submucosa is bound down tightly. They also note that in the non-specific infection the dyspnea is usually out of all proportion to the slight or moderate hoarseness. Orton *et al.*[91] (1941), however, stated that in over 50% hoarseness occurred early and was preceded or followed by a croupy cough. Later there was dyspnea, retraction, pallor and cyanosis. Jackson and Jackson[58] (1936) noted a weak or absent cough reflex. (I have observed this especially in cases of influenzal laryngotracheobronchitis and in those cases in which there was marked obstruction in the bronchi.—ED.) Baum[8] (1943) stated that with increasing obstruction the cough diminishes or disappears and there is a fall in temperature with a pale cyanosis due to diminished oxygen and circulatory exhaustion. When the obstruction is relieved the temperature rises. (I have never found a fall in temperature with increasing obstruction; on the contrary I have seen it rise and then fall after relief of the obstruction.—ED.)

Sinclair[101] (1941) describing cases of laryngitis with septicemia due to the *H. influenzæ* type B noted that the appearance of shock seemed to be out of all proportion to the short duration of the obstructive symptoms, and that after a tracheotomy most of these failed to show immediate improvement. He considers that these are the most seriously sick group. Neffson and Bullowa[85] (1938) made a similar observation in reporting a case of laryngotracheobronchitis with septicemia and meningitis due to the *H. influenzæ* and complicated by a simultaneous, bilateral, spontaneous pneumothorax.

Leigh[62] (1927) described a sudden death in a child $1\frac{1}{2}$ years old occurring during an injection of antitoxin; on postmortem examination extreme supraglottic edema was found. Beare[11] (1930) describing the symptom-

atology said, "Finally . . . . The picture may be that of a fairly quiet respiration, an alert mind, and a sudden death on attempting to sit up or after a moderate coughing seizure." Death was thought to be of cardiac origin. (The likelihood is that supraglottic edema was the cause of the sudden asphyxia; I have seen these sudden deaths due to supraglottic edema not only in a number of children, but also in several adults.—ED.)

Neffson[84] (1937) described characteristic respiratory sounds as an aid in the diagnosis of supraglottic laryngeal edema. These sounds consist of a low-pitched inspiratory stertor with a louder and lower-pitched, coarse, expiratory rattle resembling a snore. In extreme supraglottic edema, only the expiratory component may be present—namely, the loud, low-pitched, coarse rattle; on inspiration there is either a somewhat muffled, high-pitched stridor or none at all. He warns that such patients should be taken to the hospital at once for laryngoscopic confirmation of the diagnosis and usually immediate tracheotomy should be performed because of the danger of sudden asphyxia.

Diagnosis and Differential Diagnosis. As has been remarked previously, one of the main obstacles in the way of correct diagnosis has been due to the tendency to exaggerate the extent of involvement in a given instance—that is, cases of obstructive laryngitis or laryngotracheitis have been diagnosed acute laryngotracheobronchitis. Sometimes this has occurred because of the difficulty in estimating the true status, sometimes because of lack of familiarity with the problems peculiar to diagnosis in this condition, and often because of the natural propensity on the part of some of our colleagues to prove their abilities in the face of greater odds.

The diagnosis of acute laryngotracheobronchitis requires clear proof of a non-diphtheritic infection involving the larynx, trachea and bronchi and causing serious obstruction to breathing. The diagnosis of bronchial involvement must be based upon a profuse and repeated outpouring of secretions, which results in repeated blocking of the airway.

In general, acute laryngotracheobronchitis must be differentiated from diphtheritic infections, laryngeal complications of the exanthemata, allergic manifestations such as bronchial asthma, and from foreign bodies.

Neffson and Wishik[81] (1934) listed over 80 conditions which could be confused with acute laryngotracheobronchitis. They divided these under 8 headings—namely, (1) congenital malformations, (2) neuromuscular-spasmodic and paralytic, (3) tumors of the wall of the larynx or trachea, (4) occlusion by masses outside the airway, (5) plugging of the lumen by foreign matter, (6) traumatic, (7) edema of the larynx secondary to systemic disease, and (8) infectious, including blood dyscrasias.

Gilbert *et al.*[40] (1941) divided laryngeal obstructions into two groups, (1) infectious, including diphtheritic and non-diphtheritic croup; and (2) unclassified, including conditions due to allergy, foreign bodies, chemicals and other irritating agents.

Gittins[44] (1942) presented the following classification: "(1) Infectious types—(*a*) non-specific—streptococcic, staphylococcic, influenzal, pneumococcic; and (*b*) specific—diphtheria. (2) Traumatic. (3) Allergic. (4) Spasmodic."

Complications. Discussion of the complications in acute laryngotracheobronchitis, particularly those secondary to infection and septicemia, are beyond the scope of this review. However, tension pneumothorax and mediastinal emphysema, which are complications incident to acute respiratory obstruction and tracheotomy, have been receiving well-deserved prominence in recent literature and merit consideration here.

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Wilks and Moxon[115] (1875) cited 2 cases of pneumothorax following tracheotomy in which there was extensive mediastinal emphysema; they asserted that the air from the mediastinum ruptured through the pleura.

Champneys[21] (1882 and 1884) reported 19 cases of mediastinal emphysema including 4 cases of pneumothorax occurring in 56 tracheotomy cases in which death resulted. He stated, "Pneumothorax . . . . never occurred without emphysema and . . . . was probably a later sequel of the emphysema. . . . . Air was observed escaping from the mediastinum into the pleural sac. . . . . It appeared, then, that the air traveled from the tracheotomy wound into the mediastinum, which in some cases it ruptured, producing pneumothorax." He advised that postmortem examinations be performed under water in order to avoid missing a pneumothorax.

Iglauer[56] (1915) described the case of a child with severe inspiratory distress. Before opening the trachea he noted bubbles of air at the lower angle of the wound. Immediately after tracheotomy the child collapsed, became almost pulseless and had extreme pallor. Roentgenologic examination showed right-sided pneumothorax.

Wiethe[114] (1933) reported 2 cases of pneumothorax in a series of 50 tracheotomies. He stated that when respiratory obstruction is present the apex of the pleura can easily be injured while performing a low tracheotomy.

Neffson and Wishik[82] (1934) cited 4 cases of pneumothorax complicating tracheotomy and 2 cases of pneumothorax in which no tracheotomy was performed. They explained, ". . . . the air was sucked into the wound and passed alongside the trachea into the mediastinum, later rupturing through the pleura to cause the pneumothorax. All these patients had subcutaneous and mediastinal emphysema. . . . . The occurrence of such emphysema following tracheotomy is due to the fact that the obstruction . . . . was only partially relieved by the operation. As a result, the retractions continued and led to the sucking-in of air through the wound." They explained the 2 cases of spontaneous pneumothorax as follows: "Air, extravasated into the cellular tissue of the lung, spreads along the bronchi and vessels to the hilus and thence to the mediastinum . . . . it may also appear immediately subjacent to the visceral pleura. Rupture of such a vesicle leads to pneumothorax. . . . ."

Simpson[100] (1937) reported a case of pneumothorax complicating tracheotomy in fulminating laryngotracheobronchitis.

Richards[97] (1938) described 2 cases with pneumothorax. In 1 case, postmortem examination showed emphysematous blebs in the mediastinum; there was no break in the pleura; the bronchi were full of obstructive masses. The other case occurred in a 2 months old infant; there was no postmortem examination. He said, "Pneumothorax secondary to pulmonary emphysema is a complication present more frequently than hitherto appreciated."

Brennemann *et al.*[15] (1938) stated that, "Spontaneous pneumothorax may occur from rupture of an emphysematous bleb."

Neffson and Bullowa[85] (1938) described a case of bilateral tension pneumothorax and commented on the mechanism of production of pneumothorax and mediastinal emphysema as follows: "The obstruction of the bronchioles by exudate and the marked supraglottic edema combined to produce violent inspiratory efforts. The dilatation of the bronchioles caused by the strenuous inspiratory efforts and the concomitant diminution of their contractile . . . . power caused by the influenzal infection

resulted in overdistention and coalescence of the functioning pulmonary alveoli. . . . . As a result, ... certain of the emphysematous lobules burst. If they were subpleural, air passed into the pleura. . . . . If the tear is not into the pleura, the air is forced into the pulmonary interstitial tissue and travels along the loose tissue surrounding the blood- and lymph-vessels and bronchi to the root of the lung, where it either ascends between the mediastinal fascial planes and appears in the neck, spreading down from this point or, more rarely, descends into the retroperitoneal space and perirenal tissues. If there are adhesions between the visceral and the parietal pleura, air may appear in the thoracic wall without traveling down from the neck."

Michels[77] (1939) reported 5 cases of pneumothorax and 1 case of mediastinal emphysema complicating tracheotomy. Three of the cases had bilateral pneumothorax and died. Michels concluded that occurrence of pneumothorax and mediastinal emphysema can best be explained as follows: "The extrapleural route, with dissection of minute globules of air from the interstitial tissues along the vessels to the hilus, is a more common cause of their occurrence with increased intrapulmonic pressure. . . . . The dissection of air by way of the pretracheal fascia to the mediastinum, aided by the negative inspiratory pressure, affords another avenue of entry. The possibility of direct injury to the pleural dome during tracheotomy cannot be ignored."

Graebner[47] (1939) reported 3 cases of pneumomediastinum and 2 cases of pneumopericardium associated with acute obstructive laryngitis. He said, "The air was passed out of the substance of the lung and along the perivascular sheaths into the mediastinum by excess positive pressure incident to respiratory obstruction (rather than being) sucked in through the tracheotomy wound by inspiratory efforts and normal negative pressure in the mediastinum."

Dolgopol and Stern[33] (1940) described a case of pneumothorax which appeared 3 days after tracheotomy. On postmortem examination, the lungs showed alveolar emphysema, interstitial emphysema with large air bubbles in the widened, edematous interlobular septums, and air in the perilymphatic spaces. There was no mediastinal emphysema. The authors concluded that the air had traveled from the septal lymphatics to the periphery of the lung, and then escaped through rupture of pleural blebs into the pleura.

Neffson[89] (1942) reported 17 cases of pneumothorax in a series of 126 tracheotomies and gave a comprehensive discussion, including a review of the literature, of this condition. He describes the mechanism of its production as occuring *via* the following routes:

"I. *Intrinsic Route.* Increased intrapulmonic pressure caused by trapping of air results in distention and, finally, rupture of the pulmonary alveoli. . . . . Such ruptures may be microscopic, numerous and widespread or gross and limited to one area. From these ruptures the air can then spread into the following tissues: (*A*) Pulmonary interstitial tissue . . . . and thence . . . . (1) To the hilus of the lung . . . . producing mediastinal and pericardial emphysema. From the mediastinum the air can proceed . . . . (*a*) Laterally. Rupture of mediastinal blebs into the pleural cavity results in pneumothorax . . . . (*b*) Upward . . . . breaking through into the subcutaneous tissues of the neck. (*c*) Downward . . . . to the abdomen. (2) To the periphery of the lung . . . . through pleural adhesions into the pleural cavity . . . . (*B*) Subpleural tissue forming subpleural blebs which burst . . . . This is uncommon, however . . . .

"II. *Extrinsic Route.* Owing to inspiratory obstruction, the negative pressure in the thorax is increased, and air is sucked through the tracheotomy wound along the deep cervical fascia into the mediastinum . . . . From the mediastinum the air can reach the pleura, neck and abdomen in the same manner as described for the intrinsic route. This route is probably the more common after tracheotomy.

"III. *Traumatic Route.* . . . . by injury to the dome of the pleura during tracheotomy . . . . However, actually it is probably rare . . . ."

He analyzes the 17 cases of pneumothorax, ". . . . as to age, sex, site, time of occurrence after tracheotomy, relationship to previous intubation, incidence in relation to frequency of tracheotomy during various periods, time required for the disappearance of free air, mortality rates under various conditions and postmortem observations."

He finds that "The mortality rate of unilateral pneumothorax is less than 20%; that of bilateral pneumothorax, over 90%." He stresses that "early recognition and immediate treatment of this condition are life-saving. The possibility of the occurrence of tension pneumothorax must always be borne in mind and watched for after tracheotomy." Warning signs of pneumothorax and mediastinal emphysema are described, and the prophylaxis and treatment are outlined.

MacCready[73] (1944) stated, "Between 1941 and 1943 there were 6 cases of tension pneumothorax and mediastinal emphysema. Five had a preliminary bronchoscopy or the bronchoscope was passed in order to facilitate the tracheotomy. Instead of eliminating respiratory effort during the tracheotomy and hence preventing this accident from happening, these figures would suggest that it is the cause of the trouble . . . . These cases should be regarded as operative accidents." (In the light of the experience of most operators, these conclusions are untenable. Pretracheotomy bronchoscopy is advisable in order to guarantee an unhurried tracheotomy. If a bronchoscope does not relieve the dyspnea, the obstruction must be in the bronchi and bronchial aspiration should precede tracheotomy. There are some unfortunate cases in which that too is of no avail. But failure in these cases should not prejudice us against this procedure in the usual case.—ED.)

Treatment. Treatment can be divided into two main types—medical and operative. Medical treatment is made up of non-specific or supportive therapy and specific therapy; surgical treatment consists of aspiration (suction), intubation, tracheotomy and postoperative care. It is the plan of this review to discuss the advances, changes and moot questions in treatment under these separate groupings.

Medical Treatment. I. *Supportive.* A word of caution is in order at this point; we must not allow the glare of sulfonamide therapy to blind us to the value of supportive treatment, a value which cannot be overestimated.

Most authors have advised complete rest in bed, a cleansing enema, steam inhalations, mild sedation, antipyretics, plenty of fluids, and small doses of codeine to allay excessive coughing. All agree that atropine and morphine are definitely contraindicated.

Neffson and Wishik[82] (1934) stress the importance of antipyretics in order to reduce high fever, thus lowering the metabolic rate and consequently the oxygen requirement. They also advise administration of oxygen by nasal catheter or placing the patient in an oxygen tent to tide him over the acute stage for from 12 to 24 hours, when the edema usually begins to subside.

XUM

Kernan and Barach[60] (1937) advise the use of helium and oxygen under pressure.

Felts[35] (1940) recommended atmospheric supersaturation with moisture.

Davison[29,30] (1940) emphasized atmospheric temperature and humidification. By the employment of a mechanical humidifier, he raised the humidity to 95% with the temperature of 70° F. He found that loss of body water can be decreased by increasing the humidity provided that the temperature is not above 70° F. He stated that the temperature and humidity of an oxygen tent exert a greater effect on the comfort of the average patient than does the concentration of the oxygen.

Baum[8,9] (1943) suggested the use of hypertonic human plasma in order to decrease subglottic and tracheobronchial edema before surgery in urgent cases. He stated that the plasma does not cure, it merely decreases the edema. He says, "I have seen little patients showing the typical pale cyanosis of partial asphyxia with exhaustion respond in a very gratifying manner. Stridor disappears, respirations quiet down, cyanosis rapidly fades and the patient falls asleep. This all occurs within a matter of minutes after the administration of the plasma is completed. Then the entire clinical picture usually continues to improve, especially if sufficient quantities of immune serum have also been administered and the patient soon has remaining only a simple non-obstructive tracheobronchitis and laryngitis from which recovery is rapid." He also advises the use of cooled humidified oxygen. He finds that the concentrated plasma does not cause dryness, stickiness or increase plug formation; on the contrary it helps to normalize the secretions.

Holinger[53] (1944) also advised a humidity of 90% and a temperature of 70° F.; the use of 50% hypertonic glucose has been abandoned by him.

Walsh[113] (1944) recommended the use of a Burgess box in which 95% oxygen and 5% carbon dioxide is piped through an ice-box electrically driven.

Hypodermoclysis, infusions and blood transfusions have been advised by various workers.

II. *Specific.* Specific treatment has consisted of (1) vaccines and serums, (2) bacteriophage, (3) sulfonamides, (4) penicillin. Baum[3] (1928) urged the use of vaccines, pooled antistreptococcic serums and specific immune serums. Richards[96] (1933) advised the use of bacteriophage and antistreptococcic serums. Neffson and Wishik[82] (1934) used *Staph. aureus* bacteriophage in a number of cases with striking results in several.

Evans[34] (1939) used bacteriophage in order to liquefy secretions and reported 3 recovered cases—the organism was not named. In 1940, Davison,[30] Brighton[16] and Neffson[86] each recommended the use of sulfonamide therapy. Sinclair[101] (1941) reported 10 cases with *H. influenzæ* septicemia complicating acute laryngotracheobronchitis; 6 patients received adequate sulfa therapy and recovered, the other 4 did not and died.

Orton *et al.*[91] (1941) reported 38 cases in which no sulfa therapy was used; there were 9 deaths. Sulfanilamide was used in 20 cases; 13 recovered. Sulfapyridine was given to 3 patients; 2 recovered. In 15 cases sulfa therapy and surgery was needed; 7 patients recovered. In 8 cases sulfa therapy was given and no operation was needed; all recovered. They conclude, "It is possible that in many cases in which the sulfonamides were given, the disease was in a mild form . . . . We believe that, although the sulfonamides are not specific for this disease, they seem to have some value."

Neffson[88] (1942) reported that 81 cases requiring tracheotomy had been

observed since the advent of sulfa therapy. In 28 cases no chemotherapy was used; 11 deaths occurred—a mortality rate of 40%. Inadequate therapy was given in 11 cases—there was 1 death. Adequate therapy was given in 42 cases; there were 9 deaths—a mortality rate of 21%. Many patients died before they could be given the drug. Inadequate therapy was due to toxic manifestations, lack of improvement or acute aggravation of the illness. He found it difficult to draw conclusions as to the effect of the drug on the mortality rate. However, he concluded, ". . . . chemotherapy has resulted in a decrease in complications, particularly pneumonia and septicemia, and has probably lowered the mortality rate. However, the local condition has not been affected sufficiently to lessen the need for mechanical intervention."

Baum[9] (1943) advocated the use of human immune serums, especially specific influenzal convalescent serum. In 1944 he stated that sulfa therapy is unsatisfactory because the disease is not due to the streptococcus; penicillin may be of more value. He asserted, "Human immune serum is best . . . . it raises the titre of antibodies and also contains some influenza antibodies, especially after an epidemic."

Walsh[113] (1944) advises full doses of sulfadiazine intravenously or subcutaneously; 0.1 gm. per kg. body weight, totaling 0.3 gm. per kg. body weight for the first 24 hours, then 0.2 gm. per kg. per day.

Holinger[53] (1944) stated that sulfa therapy decreases the morbidity and has obviated the need for tracheotomy in many cases.

Arden and Duhig[1] (1944) reported 3 deaths in 5 tracheotomy cases in which *Staph. aureus* was recovered; sulfathiazole and sulfapyridine had been given.

MacCready[73] (1944) recommended giving sodium sulfadiazine in saline—dosage 1 gr. per pound per day, with one-half as the initial dose. The blood level should be kept at 10 to 12 mg. per 100 cc. He stated that every one of the 73 patients that received adequate sulfonamide therapy recovered except the last patient who died on the 6th day with mediastinal emphysema. He concluded, "Since the treatment of these patients is essentially the same as that of the 1933 period in all respects except for the use of the sulfonamides, any noticeable differences should be considered as resulting from the use of these drugs." (This is not strictly true because the profession has become more aware of the problems in this disease, the supportive treatment is better and postoperative care has improved considerably.—Ed.)

Surgical Treatment. Operative intervention should be resorted to only after medical treatment has failed or has been deemed inadequate. Three procedures are available, depending upon the indications, namely aspiration, intubation and tracheotomy, with direct laryngoscopy a necessary adjunct in each instance.

Laryngoscopy. Seitz[98] (1929) stated, "When done by a skilled operator, laryngoscopy will not superimpose any noteworthy degree of traumatic inflammation and an anesthetic is not required."

Neffson and Wishik[81] (1934) stated, "A direct, diagnostic laryngoscopy should be performed in every case of croup in which there is the least doubt as to the nature of the infection . . . . In skilled hands the procedure takes no more than 15 to 30 seconds, and the patient suffers very little discomfort . . . . Diagnostic laryngoscopy is indispensable . . . . in the treatment of croup."

MacCready[72] (1940) asserted, "Laryngoscopy should not be done . . . . it may precipitate an acute edema, unless one is prepared to do an imme-

diate tracheotomy." (My experience with over 2000 laryngoscopies does not bear out this observation. Moreover, the anatomy of the epiglottis is such as to hinder edema formation on the laryngeal surface, which is the surface in contact with the laryngoscope.—Ed.)

Aspiration. Lynah[69] (1916) described bronchoscopic suction in the treatment of laryngotracheobronchial obstruction, particularly diphtheritic.

Litchfield and Hardman[68] (1923) used French-woven catheters for suction of the larynx.

Gover and Hardman[46] (1923) introduced the use of metal suction tubes for tracheobronchial aspiration through the laryngoscope.

Tolle[110] (1930) reported a large series of cases in which she used Willard Parker metal suction tubes.

Neffson and Wishik[81] (1934) described a curved, spiral-tipped metal suction tube for use in bronchial aspiration through the laryngoscope. They advocated the use of suction "when the obstruction is caused by tenacious, ropy, gummy, inspissated or membranous secretions." They conclude that "the suction treatment has eliminated the need for intubation or tracheotomy in many cases and is an essential adjunct when intubation is required. It has removed the danger of sudden asphyxia which formerly attended intubation because of the jamming down of membrane . . . . or exudate . . . . by its use both morbidity and mortality have been materially reduced."

Intubation. Most authors mention intubation only to condemn it. The most emphatic denunciation that I have heard was one delivered by Dixon in a discussion of Baum's paper on the treatment of acute laryngotracheobronchitis at the 1944 A. M. A. Convention, where he said that O'Dwyer was erroneously honored for the invention of the intubation tube, because it causes suffocation from obstruction of the tube by membrane. He said that it should not be used even in diphtheria, because it has resulted in many unnecessary deaths. Apparently he has forgotten how many thousands of lives this device has saved when properly used. Intubation should always be used in conjunction with aspiration except in an emergency in which case anything possible is done at the spur of the moment. Inexperience with, misuse or abuse of intubation is no reason for condemning this procedure. There are two methods to perform an intubation: (*a*) the indirect or tactual method which is done by palpation, and (*b*) the direct or visual method through a laryngoscope. The latter is preferred in order that the underlying pathology in the larynx may be visualized at the same time.

Morris[79] (1917) reported 3 cases following measles; all 3 were tracheotomized and all 3 died. He advised intubation in these cases. (Neffson and Wishik found that intubation in measles resulted in a high mortality rate and advised tracheotomy. Apparently relief of the obstruction is not the sole answer to this problem.—Ed.)

Gittins[41] (1926), reporting 14 cases, concluded that intubation is not advisable. In 1936, he[43] reported 32 cases, of which 20 were tracheotomized with a mortality rate of 60%. Again he favored tracheotomy as compared to intubation. Hart[50] (1927) reported a case and advised that intubation be performed before tracheotomy. Baum[3] (1928) stated that he kept intubation tubes *in situ* for a period of 3 weeks when necessary. He concluded, "Intubation is the operation of choice." Codd[24] (1931) reported 2 cases and advised tracheotomy in preference to intubation. Peeler[92] (1926) believed that intubation is contraindicated in non-diphtheritic laryngitis. Bugg[17] (1931) stated that he preferred intubation to

tracheotomy. Hyde and Ruchman[55] (1931) concluded, "Intubation is not advisable because, first, the edema may be very low and the tube would not pass the swelling; second, the edema may be so marked that it is impossible to pass the tube, thereby causing injury to the tissues and resulting in a false passage and emphysema." (I saw this happen only once, in the hands of an inexperienced interne, in a patient with a cleft palate.—ED.) "A tracheotomy is advisable because in subglottic edema the chances of recovery are more rapid because of the absence of any irritating object in the larynx. If in doubt as to the cause of the edema one should institute tracheotomy instead of intubation."

Richards[96] (1933) decided in favor of tracheotomy *versus* intubation.

Neffson and Wishik[82] (1934) stated, ". . . . when the obstruction is due mainly to subglottic edema, intubation is helpful and far less dangerous than routine tracheotomy." They warned against its use in cases of supraglottic edema saying it ". . . . may give some relief but may also irritate the inflamed supraglottic tissues, causing an increase in the edema. This may cause an overlapping of the tube and may result in sudden asphyxia . . . . necessitating an immediate, urgent tracheotomy." They concluded, "However, this method of treatment is practicable only in hospitals where proper facilities and expert operators are available *at all times*."

Greenwood[48] (1939) believed that in infants a low tracheotomy conserves the laryngeal structure better than intubation.

Orton *et al.*[91] (1941) stated, "Intubation tides a patient over until a tracheotomy can be done. Intubation is a deciding factor in the reaction of dyspneic patients from respiratory shock, except in cases where there is supraglottic swelling when tracheotomy must be done at once."

Neffson[88] (1942) lists the indications, the advantages and disadvantages of intubation and concludes that ". . . . intubation performed before tracheotomy—in selected cases—is beneficial in that it gives the organism a chance to fight the acute infection before it is compelled to cope with the added burden of an operative procedure and to accustom itself to an alien respiratory mechanism and physiology, with all that this implies."

Baum[10] (1944) stated that he favors intubation over tracheotomy, since the latter results in the formation of dried plugs. He advises that after tracheotomy an intubation should be performed and the tracheotomy tube corked so that the patient can breathe through the larynx and drying will be diminished.

Holinger[53] (1944) found that intubation was not successful in his hands since it was followed by chronic laryngeal stenosis. (He did not explain what he meant by chronic laryngeal stenosis. If he implied that the patient became a chronic tube carrier, this has never occurred in my own experience.—ED.)

Tracheotomy. Most writers on this subject have signified a definite preference for tracheotomy as compared to intubation under any circumstances. Others believe that intubation should be used as a temporary measure before a tracheotomy is performed. A few still feel that intubation has an honorable place in our armamentarium and if used in properly indicated situations will obviate the need for tracheotomy and will reduce morbidity and mortality.

Smith[102] (1919) reported a case of laryngeal edema following influenza which was treated by tracheotomy with recovery. Lynch[71] (1924) reported 5 cases due to *Staph. albus* treated by tracheotomy; all recovered. Clerf[22] (1924) described a case in which 17 "life-saving" bronchoscopies

were performed following tracheotomy. He stressed the fact that plugging and not pneumonia was the most important complication. He said that in those cases where there was complete absence of cough after tracheotomy, the patients will die unless the secretions are removed mechanically.

Strachan[106] (1925) reported 3 cases in which intubation tubes were of no help and tracheotomy helped only for a little while. Postmortem examinations showed that all the bronchi were plugged. Dixon[32] (1925) reported 1 case in which a tracheotomy was done with recovery. Daily and Allen[27] (1926) described the case of an 8 year old boy who required a tracheotomy and recovered. Gittins[41,43] (1926) cited 14 cases in 10 of which tracheotomy was done; there were 6 deaths. In 1936, out of 32 cases 20 required tracheotomy; 12 of these died—a mortality rate of 60%. Leigh[62] (1927) advised tracheotomy because he thought intubation would cause ulceration.

Baum[3] (1928) stated, "Because of the dryness . . . . I have been led to the conclusion that tracheotomy has a tendency to cause too rapid evaporation of secretion increasing the difficulty of expulsion and prolonging the period of dryness with an increased tendency to bronchial plug formation. The direct blast of air coming through the tracheal cannula without the warming and moistening effect of the mucous membrane of the upper respiratory tract seems to predispose to this occurrence." (He does not mention the use of steam or medicated solutions instilled into the tracheal cannula.—Ed.)

Beare[11] (1930) writing from Australia said, "Of one thing I am convinced and that is that tracheotomy does not relieve the respiratory distress one iota. This was done on several occasions and no benefit whatever resulted." Myerson[80] (1930) in a paper describing general observations and experiences with tracheotomy, cited several cases. Thenebe[107] (1932) reported 51 cases of which 24 required tracheotomy; there were 6 deaths—a mortality rate of 25%. He urged early operation, "fearing the consequences of waiting too long." Johnson[59] (1933) reported 3 cases that were tracheotomized and recovered. He encountered much mucus plugging and advised bronchoscopic suction. Oliver and Turner[90] (1933) reported 3 cases of acute laryngeal edema complicating measles in which tracheotomy was done; there were 2 deaths.

Neffson and Wishik[82] (1934) reported 400 cases of laryngeal obstruction. tracheotomy was done in 18 of these—10 died, a mortality rate of 56%; (The general mortality rate of the entire series was 4.8%.) Brennemann *et al.*[15] (1938) concluded, "Tracheotomy is advocated as the procedure of choice unless relief can be obtained from bronchoscopic aspiration alone." Cawthorne[20] (1939) gave a good general description of the procedure of tracheotomy. MacCready[72] (1940) advocated early tracheotomy. However, he said, "Where the patients were under constant observation and it has been possible to watch them constantly many have recovered without tracheotomy." Waldapfel[112] (1940) advised removal of a segment of tracheal ring cartilage, during tracheotomy. Orton *et al.*[91] (1941) stated, "Tracheotomy is the operation of choice and should be done as soon as possible."

Gilbert *et al.*[40] (1941), finding a 60% mortality rate (4 deaths out of 6) for intubation, a 50% mortality rate (2 deaths out of 4) for intubation combined with tracheotomy, and a 20% mortality rate (1 death out of 5) for tracheotomy alone, recommended tracheotomy as the operation of choice; in the cases cited there was involvement of the larynx and trachea only. In 8 cases with laryngotracheobronchial involvement there were 7 deaths (2 out of 2 with intubation; 2 out of 2 with intubation and tracheotomy; and 3 out of 4 with tracheotomy alone).

XUM

Neffson[88] (1942) analyzed 126 cases tracheotomized because of acute obstruction of the larynx, trachea and bronchi. These occurred in a series of 1360 cases of laryngeal obstruction over a 10 year period. He found that the incidence of tracheotomy had increased from 5.3% during the first 7 years to 19.4% during the last 3 years; the mortality rate of tracheotomy fell from 50% during the first 7 years to 24.3% during the last 3 years. The mortality rate for all tracheotomized patients was 35%; the general mortality rate in the entire group of 1360 cases was 9.5%. Walsh[113] (1944) found that tracheotomy was required in 35% of his cases.

Holinger[53] (1944) stated that early tracheotomy results in lowered mortality.

Postoperative Care. Postoperative care is the more important part of tracheotomy. The most serious complication has been the formation of mucus plugs producing bronchial obstruction. All efforts in the after-care of a tracheotomy have been directed toward the prevention and removal of these plugs.

Gittins[41] (1926) advised the instillation of ". . . . adrenalin 1:10,000 in saline to soften plugs of secretion which are more troublesome than in true diphtheria." He also urged routine bronchoscopic removal of plugs before they produce obstruction and the use of an oxygen tent.

Richards[96] (1933) advised instillation of a weak solution of sodium bicarbonate into the trachea, bronchoscopic removal of plugs, a good suction apparatus at the bedside, and specially trained nurses.

Neffson and Wishik[82] (1934) stated, "Following operation the patient is placed in a cubicle, which is saturated with steam. The foot of the bed is raised in order to provide postural drainage. The tube is covered with several loose layers of gauze kept moist with warm boric acid solution. Several drops of warm 5% solution of sodium bicarbonate are dropped into the tracheotomy tube every 10 or 15 minutes for the 1st day, then less often, as necessary. Tracheal suction with a soft rubber catheter is performed every $\frac{1}{4}$ or $\frac{1}{2}$ hour for the first 2 days, then when indicated . . . . Specially trained nurses are essential for good results."

Galloway[38] (1939) advised postural irrigation using 4 to 15 cc. of 3 to 5% of warm sodium bicarbonate solution dropped into the tracheotomy tube with inspiration and the head elevated. The head is then lowered and suction applied by means of a catheter through the tracheotomy tube.

Cassidy[19] (1939) reported doing 38 bronchoscopies in a single case for the removal of plugs.

Brighton[16] (1940) instilled 1% ephedrine in normal saline solution and a sterile 5% sodium bicarbonate solution through the tracheotomy tube.

Holinger *et al.*[52] (1941) asserted that oxygen increases the viscosity of the tracheobronchial secretions and that carbon dioxide diminishes secretion by stimulating its resorption, liquefies the sputum and stimulates the cough reflex. They maintained that when oxygen is used, both steam and carbon dioxide are necessary to neutralize the drying effect of the oxygen, neither one being sufficient by itself. A concentration of 5 to 10% of carbon dioxide is used.

Neffson[88] (1942) described detailed postoperative care and urged the taking of routine roentgenograms of the chest right after tracheotomy in order to detect tension pneumothorax as soon as possible. He cites other complications following tracheotomy such as acidosis and alkalosis, extreme restlessness and convulsions, and prolonged apnea. Various difficulties in decannulation are described.

Walsh[113] (1944) instilled saline solution and neosynephrine or tuamine into the tracheotomy tube.

Baum[10] (1944) advised lavage and aspiration. He found that no solution was especially efficacious as a liquefier.

It is apparent that these cases require assiduous and continuous care to prevent the formation of plugs; once they are formed they are often very difficult to remove and present a serious hazard to life.

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DERMATOLOGY AND SYPHILOLOGY

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GRANULOMA INGUINALE

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Granuloma inguinale (venereum) has been known as a disease entity for more than 50 years. In spite of about 20 years intensive study, espe-

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cially in the United States, much confusion still exists regarding this disease, no little of which is occasioned by the great interest in a totally different process designated by a somewhat similar name, lymphogranuloma venereum. Lymphogranuloma venereum was reviewed in this Journal by Beerman, Ingraham and Stokes[6] in 1939. The following summary, presented in a more or less didactic fashion, gives the essential facts about granuloma inguinale in so far as the recent literature is concerned.

Much credit must be given to certain individuals and groups for their tireless efforts and prolonged study which have led to our better understanding of this disease. Chief among the investigators are the University of Georgia group (Torpin, Sanderson, Pund, Greenblatt, Dienst and Brandt) and the New Orleans workers (D'Aunoy and von Haam). Many others have contributed recently to individual phases of the increasing knowledge of granuloma inguinale (Goldzieher and Peck, Harris, Halty, Williamson, Howard Fox, DeMonbreun, Harry M. Robinson, Schoch and Alexander, Scott, Lyford and Johnson, Paggi and Hull, and numerous others whose work will be specifically referred to).

Definition Granuloma inguinale is a chronic specific granulomatous infection, manifested clinically by involvement of the skin and subcutaneous tissue, usually of the inguinal region, and histologically by the presence of Donovan bodies within large mononuclear cells. It is autoinoculable and only feebly transmissible.

Synonyms. Granuloma inguinale has been described under a variety of names: Granuloma venereum, granuloma genito-inguinale, granuloma pudenda tropicum, ulcerating granuloma, sclerosing granuloma, chronic venereal sores, granuloma contagiosa.

Historical Review. The disease was probably first recognized by McLeod[46] (1892) in India. He described it under the term "serpiginous ulceration of the genitals." Conyers and Daniels[14] (1896) reported cases as a separate clinical entity from British Guiana and gave accurate clinical descriptions of the disease. They named it granuloma inguinale. Galloway[27] (1897) noted a case in London. Major C. Donovan[22] (1904) demonstrated the organism which he found constantly in the lesions of patients suffering from the disease in the Madras General Hospital in India. Later Lynch[42] (1921) of Charleston isolated and cultured a gram-negative encapsulated bacillus which he felt certain was the Donovan body. Grindon[35] reported the first case in the United States in 1913, and in the 1920's numerous cases were reported from all parts of the country (Randall, Small and Belk;[62] Reed and Wolf;[64] Gage;[26] Johns and Gage;[41] Fox;[25] Schochet;[70] Symmers and Frost[78]). The infectious nature of the process was demonstrated by transmission to monkeys by DeMonbreun and Goodpasture;[18] to human beings by McIntosh[44] (1926) and more recently by Greenblatt and his associates[19,31] (1938 and 1939). Aragão and Vianna[3] of Brazil first introduced tartar emetic into the treatment for granuloma inguinale (1913) and Williamson[87] (1933) found fuadin highly successful.

Etiology. The identity of the possible causative agent of this disease has occasioned much controversy. From 1882 to 1905 it was thought to be that of tuberculosis or syphilis. Later a symbiotic infection of a spirochete and short motile rods was brought forth as the possible etiology by Butts[8] (1937). Donovan[22] (1904) reported the findings of intracellular organisms, supposedly protozoa, and since his discovery these bodies have been called the Donovan organism, or Donovan bodies. They are constantly associated with the disease, and, though accepted as diagnostic,

have not fulfilled Koch's postulates as to their etiologic rôle. These bodies have been variously interpreted as diplococci (Seibert;[72] Martini[43]), fungi (schizomycetes, Aragão and Vianna,[3] 1913), bacteria related to the *Bacillus mucosus capsulatus* group (Randall, Small and Belk;[62] Demanche and Lévy-Bruhl;[17] Poindexter[57]), as an organism related to rhinoscleroma (Goodman[29a]) and the Klebsiella group (D'Aunoy and von Haam[16]). Most authorities are in agreement that the Donovan organism, even though it might prove not to be etiologic, is of high diagnostic value in that it is constantly associated with the disease process.

Successful culture was claimed by Aragão and Vianna[3] (1913); Flu[24] (1911); Goldzieher and Peck[28] (1926); McIntosh[44] (1926–28); Walker[85] (1918); D'Aunoy and von Haam[16] (1937); Menon and his associates[47,48,49,50] (1933 and 1935). Dienst, Greenblatt and Sanderson;[19] Greenblatt, Dienst, Pund and Torpin[31] as well as Carter, Jones and Thomas[11] have denied that the true etiologic agent of the disease has been cultured, since the organisms cultured have in most instances failed to reproduce the disease. Anderson[2] (1943) working with deMonbreun's material, which was rich in Donovan bodies and with remarkably little bacterial contamination, reported the cultivation in the yolk sac of living chick embryos of a microörganism that has all the morphologic characteristics of the Donovan organism and is as yet neither cultivable on ordinary culture media nor pathogenic for mice, dogs or monkeys.

Successful transmission of the disease to animals has been reported by Menon and Annamalai,[48] deMonbreun and Goodpasture,[18] Goldzieher and Peck,[28] but denied by Campbell[9] and the University of Georgia group (Dienst, Greenblatt and Sanderson[19]), who were unable to transmit the disease to rabbits, guinea pigs, rats and mice by intraperitoneal, intratesticular or subcutaneous inoculation of material aspirated from unruptured pseudobuboes. The Georgia group[19,20,30,31,32,33,69] (1938–39) has reproduced the disease in humans by inoculation of aspirated pus from pseudobuboes of granuloma inguinale which contained no other organisms than Donovan bodies. These organisms were recovered in abundance, to the exclusion of other organisms, from the experimentally-induced lesions. The workers conclude that the Donovan bodies are strictly tissue parasites to man (Greenblatt[30]) (1943).

The organism is successfully stained by the Wright or Giemsa and by Delafield's hematoxylin method with eosin, and by silver (Dieterle[21]) impregnation method. It is characteristically seen within large mononuclear endothelial cells, has an affinity for hematoxylin, and is gram-negative. In acute fulminating lesions or in the immature stages of the development of the organism, it is not encapsulated, but acquires this with age (Sanderson[69]). The nucleus of the encapsulated body resembles a small curved bacillus and shows one or two terminal swellings simulating polar bodies, and may appear diplococcoid. Atypical forms with diphtheroid structure or appearing as non-encapsulated bacillary or diplococcoid forms surrounded by a zone of rarefaction are frequently seen. Varying interpretations of the organism's nature may be easily explained by this pleomorphism. In sections the affinity of the intracystic bodies for silver salt is characteristic, and they stain black to brown with a closed safety-pin appearance because of their elongated, ovoid and intensified polar staining reaction.

Recently Mortara and Dienst[51] (1943) reported a new method to demonstrate Donovan bodies in exudate from patients with granuloma inguinale. It is not proposed to replace Wright's stain, but is to be used in conjunc-

tion with it in doubtful cases. The new procedure demonstrates added characteristics of the Donovan body that further differentiate it from the Klebsiella group of bacteria. The authors obtained best results with the following procedure:

1. Fix smear of exudate by drying in air or gentle heating.
2. Flood smear with basic fuchsin (0.5% aqueous solution) 2 minutes.
3. Wash off excess dye with water and decolorize with citric acid (0.5% aqueous solution) until dye ceases to leave the smear (approximately 5 seconds).
4. Wash in water and counterstain with aniline blue (1% aqueous solution, 1 minute). (Aniline Blue, water soluble C. I. No. 707, National Aniline & Chemical Co.)
5. Wash, dry and examine with oil immersion lens.

If this procedure is used in dry smears from lesions of granuloma inguinale the intracellular microörganisms are stained a deep pink and the endothelial cell is stained deep blue. Extracellular Donovan bodies are also stained pink with a delicate blue outer covering. The miscellaneous bacteria and spirochetes that may be present are stained blue. Desquamated epithelial cells are not usually decolorized and remain pink. Encapsulated *K. pneumoniæ* is stained blue by this method.

The difficulty many experience in getting positive smears may be overcome by the suggestion of Weidman[86] that "there is a trick in staining for the Donovan body. When differentiating the Giemsa (or other Romanowsky) stain do not let it remain too long in the water. After staining, slide it into the water and then out promptly; otherwise the capsule becomes bleached and the Donovan body cannot be distinguished from the diplococci."

Alexander and Schoch[1] (1940) were successful in using the Giemsa stain to demonstrate the typical pathologic findings in granuloma inguinale. They conclude that it is necessary for the demonstration of the pathognomonic histologic picture of granuloma inguinale.

Geographic Incidence. The geographic distribution of the disease is wide and includes India, southern China, Australia, West Africa, the East and West Indies and most parts of North, Central and South America. Like lymphogranuloma venereum, it was formerly regarded as a tropical disease, but this is hardly a tenable view today in that cases have been noted from practically all parts of the United States. Greenblatt[30] (1943) points out that cases have been reported from almost every country and zone, from the equator to Scandinavia. As indicated by Fox[25] the number of cases reported does not give a fair idea of the prevalence of the disease in the United States. D'Aunoy and von Haam[16] (1937), also, cite numerous case reports from the literature showing the wide distribution of granuloma inguinale in the United States and believe that the reported cases are not indicative of the true incidence of this infection in the United States. Harris[39] (1930) states that the disease has been noted in this country "from Boston to San Francisco; from Portland to Savannah; as far north as Wisconsin and as far south as Georgia and New Orleans." He believes that the disease seems to travel from large seaports towards the inland sections along the great waterways.

Epidemiology. The infrequency of infection of the coital partner has led some to doubt the venereal origin of granuloma inguinale (Campbell,[9] 1928). In fact, undoubted examples of non-venereal infection with granuloma inguinale have been reported (Sidlick,[76] 1927; Campbell,[9] 1927).

XUM

Some authors have suggested the possibility of insect vector transmission. It is a relatively uncommon disease because of the difficulties of transmission. Most cases appear during the period of active sex life, but the disease has been reported in a newborn baby (Arnell and Potekin[4]); in children of 2 to 6 years of age (McLean,[45] 1911; Sabella and Wise[68]), and in an old man (94 years of age) (D'Aunoy and von Haam,[16] 1937). In the United States, negroes are affected more than whites. D'Aunoy and von Haam[16] found a ratio of 10:1 in their series of 294 cases from New Orleans. Greenblatt[30] (1943) states that of some 75 cases studied in the University of Georgia in 8 years, Donovan bodies were found in only 3 white patients. In 1 of these, the lesion was on the vulva, was self-limited and healed without therapy. Hindus are affected more frequently than Mohammedans. Thus, Menon[47] (1933) and Nair and Pandalai[54] (1934) have independently and from different sources in India reported the incidence of Hindu to Mohammedan to be 72 to 1 and 57 to 4, respectively.

Although it is generally believed that women are more often the victims of granuloma inguinale than men (Galloway;[27] Grindon[35]), D'Aunoy and von Haam found that men are affected twice as often as women. This is confirmed by other series of cases in the literature (Harris;[39] Fox[25]). It is possible that infections in women may have escaped notice because so many lesions are located on the vagina and cervix, while in the male the lesions are more conspicuous and disturbing.

Pathologic Histology. Although descriptions of the clinical processes produced by granuloma inguinale are varied, there is certain unanimity of opinion concerning the histologic changes which permit specific diagnosis from clinically suspected lesions. According to Pund and Greenblatt[59] (1937) the essential features histologically are: massive granulation tissue with numerous plasma cells, scanty lymphocytes, and scattered polymorphonuclear leukocytes with miliary collections in the papillæ, pseudo-epitheliomatous hyperplasia of the epidermis, and a pathognomonic, mononuclear cell (endothelial cell? von Haam,[84b] 1940). This cell, which permits certain histologic diagnosis, is large (25 to 90 microns in diameter), has intracytoplasmic cysts filled with deeply stained rod-like or round bodies which have an affinity for silver salts, which color them black or brown and give them a closed safety-pin appearance because of their elongated, ovoid, and intense bipolar staining reaction. von Haam and D'Aunoy[16,84] state that the histology of acute granuloma venereum is a non-specific highly vascular granulation tissue which follows a brief preliminary stage of subcutaneous infiltration and which has no characteristic appearance. In the chronic hypertrophic lesions, there is a massive development of collagenous tissue surrounding nests of plasma cells and lymphocytes.

Pathogenesis. Traditional teaching has repeatedly emphasized that granuloma inguinale is a disease of the skin and corium, and not of the lymphatics (*cf.* lymphogranuloma venereum).* The frequent inguinal location of the process, which is often preceded by a primary focus on the genitalia, led Greenblatt and his co-workers to suggest that the Donovan body spreads from an inconspicuous primary focus by way of the lymphatic system to the lymph nodes, where a temporary though mild inflammatory focal reaction with perilymphadenitis occurs. During this process, the

* Sobel and Pensky have recently reported a case of granuloma inguinale involving the lymphatics (bubonulus). (Sobel, N., and Pensky, N.: Arch. Dermat. and Syph., 48, 494, 1943.)

Donovan body reaches the papillæ and corium of the overlying skin, where an inflammatory reaction is produced. The reaction may be subacute or chronic. In 2 cases, removal of lymph nodes underneath extensive granulomatous involvement with this disease showed involvement of the lymph nodes to substantiate their viewpoint.

Location. The majority of cases occur in the inguinal region, on the external genitalia, perineum and perianal region, and to a lesser extent on the cervix,[55,59b,60] urethra, uterus,[58] tubes,[58] ovary,[58] bladder, and rectum.[5,15,16] Extragenital involvement occurs in about 6% of the cases (Greenblatt, Torpin and Pund,[33] 1938[16,25,63,76]) and includes the mouth,[16,33–36,40,52,56,67,73,77,79] face (cheek, nose),[42,67*] neck,[16,33,42,56,67] throat,[40,67] larynx and pharynx,[16,33,40] back of the hand,[12] and thigh.[73] It has occurred at the site of a skin graft.[26] Infection of the gastrointestinal tract, of the bones,[55,71] and other viscera has also been reported, but is rare. Stricture may follow involvement of the anal canal (Crane and Kimball;[15] D'Aunoy and von Haam,[16] 1937; Ault[5]), and rarely the process extends into the colon (Crane and Kimball[15]).

The incubation period of granuloma inguinale has been variously recorded from 2 days to 3 months. Greenblatt and his co-workers[19,20,30,31,32,33,69] reported an incubation period of about 21 days in experimental human inoculation, although the exact time was difficult to determine.

We propose the following adaptation of Halty's[37] classification and description of clinical symptoms:

1. *The nodular form* begins as an elevated nodule 1 to 4 cm. in diameter, is reddish in color and soft in consistency and grows to a variable size. It is usually an early manifestation and in most cases will undergo further changes, but may regress with or without treatment. Greenblatt and his co-workers[30] (1943) suggest the term "pseudobubo" for this subcutaneous nodular involvement.

2. *The ulcerovegetative form* is the most common clinical variety. It develops from the nodular type by excoriation or maceration of the superficial epithelium followed by the development of a rather spongy and easily bleeding surface covered with granulation tissue. The lesion spreads peripherally by continuity or new lesions may appear as the result of autoinoculation. In the earlier stages the granulation tissue is clean, pinkish red, the discharge serosanguineous, and the surface relatively smooth, whereas in older lesions or in grossly neglected cases, the surface becomes more uneven, the discharge seropurulent and foul smelling, and the granulation tissue changes to a grayish dirty hue. The border is sharply demarcated, indurated, and raised above the level of the skin. The process shows frequent tendency to spread along the inguinal creases and progresses slowly over weeks and months. This stage has given the disease its name. When healing takes place, atrophic depigmented scars develop with permanent loss of hair. Sometimes contact ulcers may occur in which, in the natural state, the ulcerated areas appose and are in contact with each other (Torpin, Sanderson and Brandt[83], 1939).

Secondary infection, particularly with spirochetes or aërobic or anaërobic organisms may considerably alter the picture and result in the production of deep ulceration and necrosis of the soft tissue. If a serpiginous ulcer develops on the penis, marked mutilation may result, for spread on the mucous membrane of a genital organ is more rapid than on the skin. In 55 cases of their series, D'Aunoy and von Haam[16] (1937) noted exten-

* Weiner and co-workers have reported granuloma inguinale of the eyelid. (Weiner, A. L., Gaynon, I. E., and Osherwitz, M. S.: Am. J. Ophthal., **26**, 13, 1943.)

sive necrosis of the deeper layers of the soft tissue, and particularly in colored women, extension into the rectovaginal septum with the production of rectovaginal fistulæ and perianal phlegmon. This secondary infection is usually ushered in with fever and general malaise. The usual history is that the lesion "took a sudden turn for the worse." Two patients so afflicted died, and at autopsy were found to have far-reaching cellulitis of the soft parts of the pelvis with far-advanced pyelonephritis in association with genital mutilation. Cardwell and Pund[10] record the development of carcinoma superimposed on a chronic granuloma inguinale of the cervix. Wilson[88] noted that under the influence of pregnancy the disease progressed rapidly and that these patients seemed to have a tendency to stillbirths or neonatal deaths higher than the average individual.

3. *Hypertrophic lesions* are not frequently seen. Halty[37] states that this type is distinguished by the exaggeration of the proliferative reaction. Large vegetating masses, sometimes several centimeters high, spring from the lesions simulating simple vegetation or more rarely neoplasm. These masses present a cerebriform surface with considerable débris and the discharge has a markedly fetid odor.

Elephantiasic form: Esthiomene-like pictures are now being recognized with increasing frequency as being due to granuloma inguinale, as well as lymphogranuloma venereum (D'Aunoy and von Haam;[16] Alexander and Schoch;[1] Fox[25]). This type varies from mildly hypertrophic ulceration to true elephantiasis with deep ulceration. In a differential diagnosis from lymphogranuloma venereum, D'Aunoy and von Haam[16] point out that in granuloma inguinale the swelling is associated with extensive scar formation in or around the enlarged tissue part indicating previous ulceration, whereas in lymphogranuloma venereum the skin is thick and edematous, but otherwise normal.

4. *The cicatricial type* is the result of a peculiar host reaction to the infectious agent leading to the formation of keloid-like lesions. The surface of the lesion may be compared to the relief map of a mountainous country with depressions between knobs of piled up tissue. The lesion is firm and elastic and the overlying skin may or may not show scars of previous ulceration. This keloid is not a healing or healed stage of the disease, but is a progressive lesion, since puncture will reveal the Donovan bodies and histologic examination will show small nests of inflammatory cells containing the organism embedded in dense collagenous fibrous tissue. In older cases, Cole[13] noted a tendency to cicatrization with lymphatic obstruction, which resulted in marked changes in the labia and the formation of a Hottentot apron of the clitoris.

Systemic symptoms are usually slight or absent unless there is secondary infection, deep ulceration, rectal stricture or extension of the process to the tubes or ovaries. D'Aunoy and von Haam[16] in their series noted slight discomfort, heavy discharge, itching, burning pain, urinary and rectal complaints, weakness and fever. Paggi and Hull's[55] case of metastatic granuloma venereum had very severe constitutional symptoms. In our own experience, symptoms vary from practically nothing to such severe excruciating pain that walking becomes practically impossible. Extensive ulceration may actually lead to death (Greenblatt,[30] 1943).

Complications. Granuloma inguinale may be associated with or complicated by other venereal disease. Shropshear and Hibbs[75] (1941) noted that 3 out of 7 cases of granuloma inguinale in the male, observed during the year previous to publication, were complicated by gonorrhea. Fusospirochetosis is a frequent complication of granuloma inguinale, and

syphilis, chancroid and lymphogranuloma venereum may be coëxistent. Occasionally malignancy may be superimposed (Greenblatt,[30] 1943).

Diagnosis. In 1926, Goldzieher and Peck[28] used a complement fixation test antigen from excised tissue intracutaneously injected, and scratch tests which seemed to be specific for granuloma venereum, but others (Halty,[37] D'Aunoy and von Haam[16]) deny the specificity of any serologic, allergic, or other immune reaction so far proposed. Taussig and Somogyi[80] found hyperglobulinemia in 7 cases which were examined for this. The euglobulin percentage was extremely high. This is not characteristic of the disease (*cf.* lymphogranuloma venereum). The formol gel reaction skin tests and animal inoculation are of no value in the diagnosis of granuloma inguinale (von Haam,[84a] 1938).

Diagnosis clinically is usually based upon the presenting symptoms and the identification of the Donovan bodies in smears or in tissues in association with the appearance of the "pathognomonic cell." Our routine consists of the performance of a biopsy, dividing the specimen into 2 parts, one for pathologic study, the other for smears from the deeper surfaces of the specimen, where the organisms are likely to appear more abundantly than on the surface. Giemsa or Wright stains are used for the smears, but staining with silver salts gives a characteristic closed safety-pin appearance to the organisms.

Torpin, Greenblatt and Pund[82] (1939) state that a "successful way fully to diagnose each case is to carry out the following routine, much of which is laboratory in nature: (1) Repeated Wassermann or Kahn tests to rule out syphilis; nigrosine stain[20] or darkfield study for *Treponema pallidum* and other spirochetes. (2) Smears stained for gonococci, Donovan bodies, fusospirochetes, Ducrey bacilli, yeast, etc. (3) Chancroid intradermal tests.[32] (4) Frei test. (5) Biopsy for Donovan bodies in tissue section, since not infrequently it is difficult to demonstrate these bodies in smears because of marked contamination by other organisms. The biopsy will establish the diagnosis in such cases and at the same time rule out tuberculosis, carcinoma, etc. To facilitate the diagnosis, all buboes, including the pseudo-bubo of this condition, should be aspirated under sterile conditions and routine smears and cultures made."

Treatment. For rational therapy, definite early diagnosis not only of granuloma venereum but of complications or concomitant venereal diseases must be made and proper treatment instituted. A number of methods of both local and general treatment have been proposed for granuloma venereum. All treatment methods leave a certain residue of unsuccessful cases, which by skillful combination of these methods may result in cure. Torpin and his co-workers[82] recommend 10% neoarsphenamine in equal parts of glycerin and cod-liver oil as an excellent local application to check phagedenic effects of fusospirochetosis as well as to serve as prophylaxis against such contaminants. They recommend in addition a local anesthetic such as Nupercain for its analgesic effect. Sodium perborate, potassium permanganate, tartar emetic soaks 1:1000 or a 1% tartar emetic ointment (Manson-Bahr) have been used locally.

The local use of a mixture of 20% resin of podophyllum in olive oil yielded complete cures in 102 patients treated by Tomskey, Vickery and Getzoff[81] (1942). The drug probably acts as a dehydrating agent and also has some cauterizing effect. Its use not only lessened hospital stay considerably (35%) but also the favorable response was more than twice that of those who were also treated with antimony and potassium tartrate. In treatment, secondary infection should be eliminated by cleansing the

lesion with hydrogen peroxide and hot sitz baths twice a day. The 20% resin of podophyllum in olive oil is applied to the lesion after each bath, for 5 to 7 days. Local topical analgesics are recommended for any resultant burning or pain, applied about 10 minutes before the resin of podophyllum. When the exuberant granulations have disappeared and a healthy base is evident, resin of podophyllum is discontinued and scarlet red ointment is applied following each bath to stimulate epithelization. The application of resin of podophyllum to any small resistant areas should be continued if a complete cure is to be obtained.

Potassium and antimony tartrate (*tartar emetic*) has been the standard method of treatment since its introduction by Aragão and Vianna[3] in 1913. It is given intravenously beginning with 1 to 2 cc. and gradually increasing the total dose to 10 to 15 cc. depending upon tolerance. Our experience with drug indicates that response to treatment, if it is going to occur at all, will be manifested by 2 to 3 months of treatment, at which time, if no obvious healing takes place, change of regimen should be made. Some writers caution against more than a 20 to 30 injection course, although we have not found any increase in toxicity in the continuous use of the drug for 50 to 60 injections. Toxic reactions consist of nausea, vomiting, diarrhea, arthralgia, myalgia, coughing or sneezing attacks, and occasional nitritoid reactions, and nervous spasm.

Fuadin, named after Fuad I, late King of Egypt, an intramuscularly administered antimony compound, was introduced into the treatment of granuloma inguinale by Williamson and co-workers[87] in 1933, following their observation of its remarkable efficacy in the treatment of bilharziasis. The compound was originally devised by Khlil, and is sodium antimony iii biscatechol disulfonate of sodium. Fuadin can be used in cases in which tartar emetic cannot be tolerated because of reaction, or in cases in which tartar emetic has failed. Williamson and co-workers recommend a 7% solution with dose beginning with about 1.5 cc. and gradually being increased every 1 to 2 days up to 5 cc. intramuscularly. They reported 14 cases with excellent results superior to those obtained with tartar emetic. Rajam[61] (1934) considered it effective and more toxic. Shattuck, Little and Coughlin[74] found sodium antimony thioglycollate and antimony thioglycolic acid effective drugs. Anthiomaline (lithium antimonio-thiomalate) has also been tried (Robertson and Sharp[65]). Hanschell[38] reports the enhancement of the antimony effect by combining its use with fever therapy, Nair and Pandalai[54] by non-specific therapy, and Earle[23] by the combination of Fuadin and sulfanilamide. Treatment should be continued for at least 2 months after complete healing in order to avoid relapse, which is unfortunately too prone to occur. Favorable response to chemotherapeutic agents is roughly inversely proportional to the duration of this infection, although at times surprisingly good results are obtained in long-standing cases (*cf.* Brandt and Gatewood[7]).

In the event of failure of chemotherapeutic agents, physical and surgical methods may have to be employed. Preliminary roentgen ray irradiation may be followed by electrosurgical excision and further roentgen ray treatment. Greenwood[34] in an analysis of 22 cases states that fulguration of the edges of the advancing border of the lesion plus cleanliness resulted in complete healing of all cases within 70 days. Murray[53] reports the successful use of ultraviolet irradiation. Robinson and co-workers[66] (1942) propose surgery for many cases previously considered hopeless. Their results are in some cases truly amazing.

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BOOK REVIEWS AND NOTICES

NEW BOOKS

Annual Review of Biochemistry. By JAMES MURRAY LUCK, Editor, Stanford Univ., and JAMES H. C. SMITH, Associate Editor, Carnegie Institution of Washington, Division of Plant Biology, Stanford Univ., California. Vol. 13. Pp. 795. California: Stanford Univ. P. O., Annual Reviews, Inc., 1944. Price, $5.00.

X-ray Examination of the Stomach. A Description of the Roentgenologic Anatomy, Physiology, and Pathology of the Esophagus, Stomach, and Duodenum. By FREDERIC E. TEMPLETON, M.D., Head of the Dept. of Roentgenology, The Cleveland Clinic. Formerly Associate Professor of Roentgenology at the Univ. of Chicago. Pp. 516; 297 figs. Chicago: Univ. of Chicago Press, 1944. Price, $10.00.

Medical Clinics of North America. The Mayo Clinic Number. Symposium on Chemotherapy. By 36 Contributors. Pp. 789–1028; 75 figs. Philadelphia and London, Saunders, 1944. Price, $16.00 per year.

A Source-book of Biological Names and Terms. By EDMUND C. JAEGER, Riverside Junior Coll., Riverside, Calif. Pp. 256. Springfield, Ill.: Thomas, 1944. Price, $3.50.

Surgical Disorders of the Chest. Diagnosis and Treatment. By J. K. DONALDSON, B.S., M.D., F.A.C.S., MAJOR, M.C., A.U.S.; Diplomate, American Board of Surgery; Associate Professor of Surgery and in charge of Thoracic Surgery, Univ. of Arkansas School of Medicine, etc.; Surgical Staff, St. Vincent's Infirmary, and Visiting Staff, Baptist Hospital, Little Rock, Ark. Formerly Chest Surgeon to Arkansas State Hospital for Nervous Diseases; Associate Surgeon, Robert B. Green Hospital, Visiting Surgeon to Santa Rosa, Nix, and Medical Arts Hospitals, San Antonio, Texas. Pp. 364; 127 figs. Philadelphia: Lea & Febiger, 1944. Price, $6.50.

Minor Surgery. Edited by HUMPHRY ROLLESTON and ALAN MONCRIEFF. Pp. 174. New York: Philosophical Library, 1944. Price, $5.00.

Mitosis. The Movements of Chromosomes in Cell Division. By FRANZ SCHRADER, Professor of Zoölogy, Columbia Univ. Pp. 110; 15 figs. New York: Columbia Univ. Press, 1944. Price, $2.00.

The Gastro-intestinal Tract. A Handbook of Roentgen Diagnosis. By FRED JENNER HODGES, B.S., M.D., Professor of Roentgenology, Univ. of Michigan, Medical School, Ann Arbor, Mich. Pp. 320; numerous illustrations. Chicago: Year Book Publishers, 1944. Price, $5.50.

A New German-English Psycho-analytical Vocabulary. Research Supplements to the International Journal of Psycho-analysis, No. 1. By ALIX STRACHEY. Published for The Institute of Psycho-analysis. Pp. 84. Baltimore, Williams & Wilkins, 1943. Price, $2.50.

Manual of Psychological Medicine. For Practitioners and Students. By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S.E., Consulting Physician to Univ. College Hospital; London Lecturer on Mental Deficiency, London Univ. Pp. 298. Baltimore: Williams & Wilkins, 1943. Price, $5.00.

Rehabilitation, Re-education and Remedial Exercises. By OLIVE F. GUTHRIE SMITH, M.B.E., C.S.M.M.G., T.M.G., Principal of the Swedish Institute, London; Director of the Physical Exercise Dept., St. Mary's Hospital, W. 2; Member of the Council of the Chartered Society of Physiotherapists. FOREWORD by LORD HORDER, G.C.V.O., M.D., F.R.C.P. Pp. 424; 273 figs. Baltimore: Williams & Wilkins, 1943. Price, $6.00.

The Baby Manual. A Practical Guide From Early Pregnancy Through the Second Year of Life. By HERMAN N. BUNDESEN, M.D. Foreword by THOMAS PARRAN, M.D., Surgeon General, U.S.P.H.S. Pp. 590; 137 figs. New York: Simon & Schuster, 1944. Price, $3.00.

Global Epidemiology. A Geography of Disease and Sanitation. By JAMES STEVENS SIMMONS, B.S., M.D., PH.D., DR. P.H., Sc.D. (HON.), Brigadier General, U. S. Army; Chief, Prev. Med. Serv., Office of the Surgeon General, U. S. Army; Member, Nat'l Res. Cn. and Comm. on Med. Res., O.S.R.D.; Lecturer, Dept. of Prev. Med., Johns Hopkins Univ. Med. School; Lecturer in Public Health, Yale Univ. School of Med.; Professional Lecturer in Prev. Med., George Washington Univ. Med. School; Member, Visiting Comm., Harvard School of Public Health; Lecturer in Tropical Medicine, Army Medical School; TOM F. WHAYNE, A.B., M.D., LT. COL., M.C., A.U.S., formerly Director, Medical Intelligence Div., Prev. Med. Serv., Office of the Surgeon General, U. S. Army; GAYLORD WEST ANDERSON, A.B., M.D., DR. P.H., LT. COL., M.C., A.U.S., Director, Med. Intelligence Div., Prev. Med. Service, Office of the Surgeon General, U. S. Army; Director, School of Public Health, Univ. of Minnesota; HAROLD MACLACHLAN HORACK, B.S., M.D., MAJOR, M.C., A.U.S., Chief, Dissemination Brance, Medical Intelligence Div., Prev. Med. Serv., Office of the Surgeon General, U. S. Army; Instructor in Medicine, Duke Univ. School of Med.; and COLLABORATORS. Vol. 1. Part 1: India and the Far East; Part 2: The Pacific Area. Pp. 504. Philadelphia, London, Montreal: Lippincott, 1944. Price, $7.00.

NEW EDITIONS

The Art of Anesthesia. By PALUEL J. FLAGG, M.D., Visiting Anesthetist to Manhattan Eye and Ear Hospital; Consulting Anesthetist to St. Vincent's Hosp., New York, N. Y.; Consulting Anesthetist to the Women's Hosp., Sea View Hosp., Jamaica Hosp., Mount Vernon Hosp., Flushing Hosp., Mary Immaculate Hosp., St. Mary's Hosp., Far Rockaway, N. Y.; Nassau Hosp., L. I.; Director of Pneumatology, World's Fair, New York City, and Chairman of Committee on Asphyxia of the American Medical Association. Seventh Ed. Pp. 519; 166 illus. Philadelphia, London, Montreal: Lippincott, 1944. Price, $6.00.

Heart Disease. By PAUL DUDLEY WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician to the Massachusetts General Hosp., Boston. Third Ed. Dedication to The Friendship and Collaboration of the Medical Profession of All The World. Pp. 1025; 138 figs. New York: Macmillan, 1944. Price, $9.00.

Technical Methods for the Technician. By ANSON LEE BROWN, A.B., M.D., Director of Dr. Brown's Clinical Laboratory and Dr. Brown's School for Technicians, Columbus, Ohio. Pp. 706. Third Ed. 229 figs. Published by the Author, 1944. Price, $10.00.

Bailey's Textbook of Histology. Revised by PHILIP E. SMITH, PH.D., Professor of Anatomy, College of Physicians and Surgeons, Columbia Univ.; and WILFRED M. COPENHAVER, PH.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia Univ., with the assistance of AURA E. SEVERINGHAUS, PH.D., Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia Univ., and CHARLES M. GOSS, M.D., Professor of Anatomy, Univ. of Alabama Medical School. Eleventh Ed. Pp. 786; 470 figs. Baltimore: Williams & Wilkins, 1944. Price, $6.00.

Practical Methods in Biochemistry. By FREDERICK C. KOCH, Frank P. Hixon Distinguished Service Professor Emeritus of Biochemistry, Univ. of Chicago; Director of Biochemical Research, Armour & Co., Chicago; and MARTIN E. HANKE, Associate Professor of Biochemistry, Univ. of Chicago. Fourth Ed. Pp. 353; 20 figs.; 40 tables. Baltimore: Williams & Wilkins, 1943. Price, $2.25.

Theory of Occupational Therapy. By NORAH A. HAWORTH, M.A. (CANTAB.), M.R.C.S., L.R.C.P., D.P.M., Assistant Med. Officer, London Passenger Transport Bd., late Med. Officer, Horton Emergency Hosp., and Senior Assistant Med. Officer, Severalls Mental Hosp., Colchester; and E. MARY MACDONALD, Prin., Dorset House School of Occupational Therapy, Barnsley Hall Emergency Hosp., Bromsgrove. Member of the Assn. of Occupational Therapists. Second Ed. Pp. 148; 68 figs. Baltimore: Williams & Wilkins, 1944. Price, $2.50.

A Laboratory Manual of Physiological Chemistry. By D. WRIGHT WILSON, Benjamin Rush Professor of Physiological Chemistry, Univ. of Penna. Pp. 269. Fifth Ed. Baltimore: Williams & Wilkins, 1944. Price, $2.50.

The Standardization of Volumetric Solutions. By R. B. BRADSTREET, M.S. Second Ed. Pp. 151; numerous figs. and tables. New York: Chemical Publishing Co., 1944. Price, $3.75.

Fundamentals of Anesthesia. An Outline. By SUBCOMMITTEE ON ANESTHESIA OF DIVISION OF MEDICAL SCIENCES, NATIONAL RESEARCH COUNCIL. Second Ed. Pp. 231; 81 figs.; 19 tables. Illinois: American Medical Assn. Press, 1944. Price, $2.50.

The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D. Fourth Ed. St. Louis: Mosby, 1944. Price, $10.00.

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H. S.

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